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(54)PYRIDINE DERIVATIVE SUBSTITUTED BY HETEROCYCLE AND FUNGICIDE CONTAINING THE SAME

(57) An object of the present invention is to provide an antifungal agent which has excellent antifungal effects and is superior in terms of its physical properties, safety and metabolic stability. According to the present invention, there is disclosed a compound represented by the following formula (I), or a salt thereof:

wherein R1 represents a hydrogen atom, a halogen atom, an amino group, a $C_{1:6}$ alkyl group, a $C_{1:6}$ alkoyz group or a $C_{1:6}$ alkyl group, a R1 and R1 and R1 alkyl group, a represent a hydrogen atom, a $C_{1:6}$ alkyl group, a marino group or a di $C_{1:6}$ alkylarino group, one of X and Y is a nitrogen atom while the other is a nitrogen atom or an oxygen atom; ring A perpensents a 5 or 6-momber heteroary/ring or a benzene ring which may have a halogen atom, or 1 or 2 $C_{1:6}$ alkyl groups, Z represents a single bond, a methylene group, an ethylene group, an ethylene group, an ethylene group, an explain atom, a suffur atom, $C_{1:6}$ alkyl group, a $C_{1:6}$ alkyl group, a C

Description

Field of the Invention

[0001] The present invention relates to heterocyclic substituted pyridine derivatives and to antifungal agents comprising the same.

Description of the Related Art

10 [0002] In recent years, managements of opportunistic infections have become more and more significant more than ever because of an increase in the number of elderly people and immunocompromised patients as a result of advanced chemotherapies or the like. As demonstrated by the fact that opportunistic infections are occurring one after another by different advulent patingen, it is shown that the problem of infectious disease will not ends as long as there are underlying diseases that diminish the immune functions or patients. Consequently, new strategies for infectious diseases control. including the problem of drug-resistant pathogen, will be one of the important issue in the soon-to-come aged society. [0003] In the field of antifungal agents, heretofors, for instance, amphotericine B which is based on a polyene skeleton, fluconazole in traconazole and vorionazole which are based on an azole skeleton, the like, have been developed for

the treatment of deep seated mycoses. Most of pre-existing drugs already available commercially have similar mechanism of action, and currently, the appearance of azole-resistant fungl or the like has been problems.

[0004] In recent years, as a 1,5-β-glucan synthetase inhibitor with a novel mechanism, naturally occurring compound-derived cyclic hexapeptides caspofungin and micallungin or the like, have been developed; however, from the fact that these agents only exist in lipiticable form, they are not yet sufficient practically as artifluring algents.

[0005] Since there have been the situations that the pre-existing antifungal agents are insufficient for treatment of the deep seated mycoses, there is a demand and need for development of agents which are based on a novel mechanism and are of high safety.

[0005] As the related art relevant to antifungal agents based on such a novel mechanism, Patent Documents 1 and 2 describe pyridine derivatives which demonstrates effects against the onset, progress, and persistence of infections by inhibiting the expression of cell wall proteins, inhibiting the cell wall assembly and also adhesion onto cells, and preventing pathogens from showing pathogenicity, with the process which transports GPI (Glycosylphosphatidylinosito)-anchored proteins to the cell wall being inhibited.

[0007] However, groups of the compounds disclosed in Patent Document 1 have 2-benzyl pyridine moleties as the common structure, clearly differing structurally from compounds according to the present invention. In addition, the groups of the compounds disclosed in Patent Document 1 bear the problem that, although these compounds demonstrate activities in vitro, they are easily metabolized inside the body. The group of compounds disclosed in Patent Document 2 exhibits excellent antifungal activity, but the group of representative compounds has the structure represented by the following formula:



A1 = optionally substituted 3-pyridyl or quinclyl, etc.

X1 = -C(=O)-NH, -NH-C(=O)-, etc.

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E = furyl, thienyl, pyrrolyl, phenyl, pyridyl, tetrazolyl, thiazolyl, or pyrazolyl

Looking only at those having pyridine ring skeletons, this group differs structurally from the compounds according to the present invention in that the common structure has a single ring bound via an amidemethylene linker at the pyridine ring 3-position.

[0008] Patent Documents 3 to 5 also provide examples of related art with structures similar to the compounds according to the present invention. Patent Documents 3 and 4 describe pyridine derivatives substituted by a pyrazole ring, which are used as glycine transporter inhibitors or 5-HT receptor ligands, white Patent Document 5 describes 5-member heterocyclic substituted pyridine derivatives which are used as an AGE disruptor and hibitor.

56 [0009] However, Patent Documents 3 to 5 do not disclose the compounds according to the present invention, and the antifungal effects of the compounds disclosed in Patent Documents 3 to 5 against Candida, Aspergillus, Cryptococcus and the like which are common fungi in human fungal disease are not disclosed.

[Patent Document 1] International Publication WO 02/04826 pamphlet [Patent Document 2] International Publication WO 05/033079 pamphlet [Patent Document 3] International Publication WO 03/031435 pamphlet [Patent Document 4] International Publication WO 04/089931 pamphlet Patent Document 51 International Publication WO 04/086997 pamphlet

Disclosure of Invention

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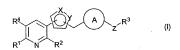
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Problems to be Solved by the Invention

[0010] It is an object of the present invention to provide an antifungal agent which has excellent antifungal action not found in the antifungal agents in the prior art, and which is also excellent in terms of property, safety and metabolic stability.

Means for Solving the Problems

[0011] As a result of exhaustive research conducted in view of the above circumstances, the present inventors have succeeded in synthesizing novel pyridine derivatives (hereinafter, the compounds of the present invention) represented by the following formula (ii):



and having a chemical structure in which a pyridine ring and a 5- or 6-member heteroaryl ring or benzene ring are joined with a 5-member heteroayl methyl group as a linker, and have perfected the present invention upon discovering that these compounds have excellent artiflungial action.

[0012] That is, the present invention provides:

[1] a compound represented by the following formula (I), or a salt thereof:

wherein R1 represents a hydrogen atom, a halogen atom, an amino group, R1-MH-(wherein R11 represents a $C_{1,0}$ alloyl group, a hydroxy $C_{1,0}$ alloyl group, a hydroxy $C_{1,0}$ alloyl group, or a $C_{1,0}$ alloysycathonyl $C_{1,0}$ alloyl group, a $C_{1,0}$ alloyl group, a minogroup or a $C_{1,0}$ alloyl group, a $C_{1,0}$ alloyl group, a minogroup or a $C_{1,0}$ alloyl group, a $C_{1,0}$ alloyl group, a minogroup or a $C_{1,0}$ alloyl group, a $C_{1,0}$ alloyl group, a minogroup or a $C_{1,0}$ alloyl group, a $C_{1,0}$ alloyl group, a minogroup or a $C_{1,0}$ alloyl group, a $C_{1,0}$ alloyl group, a minogroup or a $C_{1,0}$ alloyl group, a $C_{1,0}$ alloyl group, a minogroup or a $C_{1,0}$ alloyl group, a $C_{1,0}$ alloyl group, a minogroup or a $C_{1,0}$ alloyl group, a $C_{1,0}$

one of X and Y is a nitrogen atom while the other is a nitrogen atom or an oxygen atom;

ring A represents a 5- or 6-member heteroaryl ring or a benzene ring which may have 1 or 2 halogen atoms, or 1 or 2 C_{1-6} alkyl groups;

Z represents a single bond, a methylene group, an ethylene group, an oxygen atom, a sulfur atom, -CH₂O-, -OCH₂-, -NH-, -CH₂NH-, -NHCH₂-, -CH₂S-, or -SCH₂-;

 $\rm R^3$ represents a hydrogen atom, a halogen atom, a $\rm C_{1.6}$ alkyl group, a $\rm C_{8.8}$ cycloalkyl group, a $\rm C_{6.10}$ aryl group, a 5- or 6-member non-aromatic heterocyclic group which may have 1 or

2 substituents selected from substituent group $\alpha\!:$ and

[substituent group α]

substituent group α represents the group consisting of a halogen atom, a cyano group, a C_{1.6} alkyl group, a

 $C_{1.6}$ alkoxy group, a $C_{1.6}$ alkoxycarbonyl group, a $C_{3.8}$ cycloalkyl group, a $C_{2.6}$ alkenyl group and a $C_{2.6}$ alkynyl group.

R4 represents a hydrogen atom or a halogen atom:

excluding compounds where all of R¹, R², and R⁴ represent the hydrogen atom at the same time when Z represents the signle bond or R³ represents the hydrogen atom;

[2] a compound represented by the following formula (I'), or a salt thereof:

$$\begin{array}{c|c} X \\ Y \\ A \\ Z \\ R^3 \end{array} \qquad (I')$$

wherein R¹ represents a hydrogen atom, a halogen atom, an amino group, a $C_{1.6}$ alkyl group, a $C_{1.6}$ alkyl group; a $C_{1.6}$ alkyl group;

R2 represents a hydrogen atom or an amino group:

one of X and Y is a nitrogen atom while the other is a nitrogen atom or an oxygen atom;

ring A represents a 5- or 6-member heteroaryl ring or a benzene ring;

Z represents a methylene group, an oxygen atom, $-CH_2O_1$, $-OCH_{2^{-1}}$, -NH, $-NHCH_{2^{-1}}$ or $-CH_2NH$; and R^3 represents a C_1 -ealityl group, a C_2 -explosibly group, a C_3 -exploring top or a 5- or 6-member heteroaryl group which may have 1 or 2 substituents selected from substituent group C_1 .

[substituent group α]

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substituent group α represents the group consisting of a halogen atom, a C_{1.6} alkyl group, a C_{1.6} alkoxy group, a C_{3.6} cycloalkyl group, a C_{2.6} alkenyl group and a C_{2.6} alkynyl group;

[3] the compound according to item [1] or [2], or the salt thereof, wherein a partial structure represented by formula (II):

in the compound represented by the formula (I) or the formula (I'):

$$\begin{array}{c|c}
R^4 & X & A \\
R^1 & N & R^2
\end{array}$$
(1)

$$\begin{array}{cccc}
X & & & & & & & & \\
X & & & & & & & & \\
X & & & & & & & & \\
R^1 & & & & & & & & \\
R^2 & & & & & & & & \\
\end{array}$$

is a partial structure selected from the group consisting of:

[4] the compound according to item [1] or [2], or the salt thereof, wherein one of X and Y is a nitrogen atom and the other is an oxygen atom; [5] the compound according to item [4] or the salt thereof, wherein a partial structure represented by the formula (II):

in the compound represented by the formula (I) or the formula (I'):

$$\begin{array}{c|c}
R^4 & X & A \\
R^1 & N & R^2
\end{array}$$
(1)

$$\begin{array}{c|c}
X \\
Y \\
A \\
Z
\end{array}$$

$$\begin{array}{c}
R^3 \\
\end{array}$$

$$\begin{array}{c}
(I')
\end{array}$$

is a partial structure represented by the following formula (III):

or a partial structure represented by the following formula (IV):

[6] the compound according to item [1] or [2], or the salt thereof, wherein X and Y are both nitrogen atoms; [7] the compound according to item [6] or the salt thereof, wherein a partial structure represented by the formula (II):

in the compound represented by the formula (I) or the formula (I'):

$$\begin{array}{c|c}
R^4 & X & A & Z & R^3 \\
R^1 & N & R^2 & R^3
\end{array}$$
(I)

is a partial structure represented by the following formula (V):

or a partial structure represented by the following formula (VI):

- [8] the compound according to any one of items [1] to [7] or the salt thereof, wherein R² represents an amino group; [9] the compound according to item [8] or the salt thereof, wherein R¹ represents a hydrogen atom, an amino group or a C₁ c₂ allowy C₁ allowy Group:
- [10] the compound according to any one of items [1] to [7] or the salt thereof, wherein R¹ represents an amino group and R² represents a hydrogen atom;
 - [11] the compound according to any one of items [1] to [10] or the salt thereof, wherein the ring A represents a pyridine ring, a benzene ring, a furan ring, a thiophene ring or a pyrrole ring;
- [12] the compound according to item [11] or a salt thereof, wherein ring A represents a pyridine ring or a benzene
- ring;
 - [13] the compound according to any one of items [1] to [12] or the salt thereof, wherein Z represents an oxygen atom. -CH₀O- or -OCH₀-:
 - [14] a pharmaceutical composition comprising the compound according to any one of items [1] to [13] or the salt thereof
 - [15] a medicament comprising the compound according to any one of items [1] to
 - [13] or the salt thereof:

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- [16] an antifungal agent comprising the compound according to any one of items [1] to [13] or the salt thereof,
- as an active ingredient;
 [17] a method for preventing and/or treating a fungal infection comprising administering a pharmacologically
 effective obsec of the compound according to any one of items [1] to [13] or the salt thereof:
- [18] a use of the compound according to any one of items [1] to [13] or the salt thereof for manufacturing an antifungal agent.

Advantageous Effects of the Invention

- [0013] The compound (I) of the present invention or a sat thereof 1) acts against the onset, development and persistence of infections by inhibiting rungal GPI biosynthesis, thereby inhibiting expression of cell wall proteins and blocking call wall assembly while preventing the fungus from attaching to cells so that the pathogen cannot become pathogenic, and 2) is superior in terms of physical properties, safety and metabolic stability, and is extremely useful as a preventive or thereactic acent for funcal infections.
- Best Mode for Carrying Out the Invention
 - [0014] The present invention is explained below in more detail by reference to the symbols and the terms used herein being defined and the following examples.
- 36 [0015] Herein, a structural formula of a compound sometimes represents a certain isomer for convenience of description. However, compounds according to the present invention may include all possible isomers, such as structurally possible geometric isomers, optical isomers generated due to the presence of asymmetric carbons, stereoisomers, tautomers, and microres of isomers, and are not limited to formulae being used for the convenience of description, and may be either one of two isomers or a mixture of both isomers. Thus, the compounds according to the present invention are yet beither optically active compounds having an asymmetric carbon atom in their molecules of their racemates, and are not restricted to either of them but include both. Furthermore, the compounds according to the present invention may exhibit crystalline polymorphism, but likewise are not restricted to any one of these, but may be in any one of these crystal forms or exist as a mixture of two or more crystal forms. The compounds according to the present invention also include both anythyrous and solvates such as hydrated forms.
- (9016) The term "C_{1,4} allyl group" used in the present specification refers to a straight-chain or branched-chain aliving up with 1 to 6 carbon atoms which is a monovalent group induced by removal of any one hydrogen atom from an aliphatic hydrocarbon with 1 to 6 carbon atoms. Specifically, examples of "C_{1,4} alkyl group" includes a methyl group, an erbyl group, an export group, an isoponyl group, an exporting group, an expently group, an expently group, an expently group, a exhebyl group, a exhethyl group, an exhethyl group, a exhethyl group, an exhethyl group, and exhethyl gro
 - group, a n-butyl group, an isobutyl group, a sec-butyl group or a terb-butyl group or the like.

 [0017] The term "Co_p alkenyl group" used in the present specification refers to a straight-chain or branched-chain
 alkenyl group with 2 to 8 carbon atoms which may contain 1 or 2 double bonds. Specifically, exemples of "Co_p alkenyl
 group" include an ethernyl group, a 1-propenyl group, a 2-propenyl group, a 2-bropenyl group gr

- butenyl group, a 2-methyl-1-propenyl group, a pentenyl group, a 3-methyl-2-butenyl group, a hexenyl group, a hexanedienyl group or the like, preferably an ethenyl group, a 1-propenyl group, a 2-propenyl group, a 1-butenyl group, a 2-butenyl group, a 3-butenyl group, a 2-butenyl group, a 2-butenyl group, a 2-butenyl group, a 2-butenyl group, a 3-butenyl group, a 3-butenyl group, a 3-butenyl group a 3-butenyl group, a 3-butenyl group, a 3-butenyl group, a 3-butenyl group a 3-
- [0018] The term 'C_{2,8} alkynyl group' used in the present specification refers to a straight-chain or branched-chain alkynyl chain with 2 to 6 carbon atoms which may contain 1 or 2 triple bonds. Specifically, examples of 'C_{2,8} alkynyl group, a relative production and extra the strain of the
- [0019] The term 'C_{3.6} cycloalkyl group' used in the present specification refers to a cyclic alighatic hydrocarbon group.
 10 with 3 to 8 carbon atoms. Specifically, examples of 'C_{3.6} cycloalkyl group' include a cyclopropyl group, a cycloburyl group, a cyclohexyl group or the like, preferably a cyclopropyl group.
 - [0020] The term "C₁₋₆ alkoxy group" used in the present specification referes to a group in which an oxygen atom is bonded to terminus of the "C₁₋₆ alkoxy group" defined above. Specifically, examples of "C₁₋₆ alkoxy group, a nichotod group, an elenbuty group, a nebotutoxy group, a nebotutoxy group, a nepentyloxy group, a nechotoxy group, a nerhyloxy group, a nechyloxy group, a nechylo
- [0021] The term "hydroxyl C₁₋₆ alkyl group" used in the present specification refers to a group in which any of the
 45 hydrogen atoms in a "C₁₋₆ alkyl group" as defined above has been replaced by a hydroxyl group. Specifically, examples
 of "hydroxyl-0-1-6, alkyl group" include a hydroxymethyl group, a 1-hydroxyethyl group, a 2-hydroxyl-spropyl group, a 2-hydroxy-is-propyl group, a 2-hydroxy-is-propyl group, a 2-hydroxy-is-propyl group, a 1-hydroxy-is-propyl group, a 1-hydroxy-is-propyl group, a 2-hydroxy-is-propyl group, a 2-hydroxy-is-propyl group, a 2-hydroxy-is-propyl group, a 2-hydroxy-is-propyl group or the like, preferably a hydroxy-is-propyl group, a 2-hydroxy-is-propyl group or the like, preferably a hydroxy-is-propyl group.

isobutoxy group, a sec-butoxy group, a tert-butoxy group or the like.

- 30 [0022] The term "C_{1,6} alkoxycarbonyl group" used in the present specification refers to a group in which a carbonyl group is bonded to terminus of the "C_{1,6} alkoxy group" defined above. Specifically, exemples of "C_{1,6} alkoxycarbonyl group," include a methoxycarbonyl group, an ethoxycarbonyl group, an ethoxycarbonyl group, an appropoxycarbonyl group, an isopropoxycarbonyl group.
 - [0023] The term "C_{1.6} alkoxycarbonyl C_{1.6} alkyl group" used in the present specification refers to a group in which the
 "C_{1.6} alkyl group" defined above is bonded to terminus of the "C_{1.6} alkoxycarbonyl group" defined above. Specifically, examples of the "C_{1.6} alkoxycarbonyl C_{1.6} alkyl group" include a methoxycarbonyl group, a methoxycarbonyl ethyl group, an ethoxycarbonyl methyl group, an ethoxycarbonyl methyl group or the like.
- [0024] The term "C₆₋₁₀ any igroup" used in the present specification refers to an aromatic hydrocarbon cyclic group with 6 to 10 carbon atoms. Specifically, examples of "C₆₋₁₀ any igroup" include a phenyl group, a 1-naphthyl group, a 2-0 naphthyl group, an indenyl group, an azulenyl group, a heptalenyl group or the like, preferably a phenyl group, a 1-naphthyl group. 2-naphthyl group or the like.
- [0025] The term "C₁₋₆ alkoxy C₁₋₆ alkyl group" used in the present specification refers to a group in which any of the hydrogen atoms in a "C₁₋₆ alkyl group" as defined above has been replaced by a "C₁₋₆ alkoxy group" as defined above. Specifically, examples of "C₁₋₆ alkoxy C₁₋₆ alkyl group" include a methoxymethyl group, an ethoxymethyl group or the like.
- [0026] The term "halogen atom" used in the present specification refers a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.
- [0027] The term "hetero atom" used in the present specification refers to a nitrogen atom, a sulfur atom or an oxygen
- [0028] The term "5- or 6-member heteroaryl ring" used in the present specification refers to an aromatic ring in which the number of atoms making up the ring is 5 or 6, and 1 or more hetero atoms are included in the atoms making up the ring. Specifically, examples of 5'- or 6-member heteroaryl ring" rinduce a furan ring, a thiophene ring, a pyriddine pyriddine ring, a pyrazine ring, a pyridazine ring, a pyrimidine ring, a triazole ring (a 1,2,3-triazole ring, a 1,2,4-triazole ring, etc.), a thiazole ring, a pyrazine ring, are of the ring at the ring at reference or ring, etc.), a thiazole ring, a pyrazole ring, an oxazole ring, an isoxazole ring, an isoxazole ring, an avoitazole ring, are thiadiazole ring or the like.
- [0029] The term "5- or 6-member heteroaryl group" used in the present specification refers to a monovalent group induced by removing 1 hydrogen atom from any position in an aromatic ning in which the number of atoms making up the ring is 5 or 6 and 1 or more hetero atoms are included in the atoms making up to the ring. Specifically, examples of 5-

or 6-member hetercaryl group, include a lunyl group (a 2-funyl group or a 3-funyl group, etc.), a thientyl group (a 2-flientyl group or a 3-flientyl group, etc.), a pyrradyl group or a 3-flientyl group, a 3-pyrradyl group, a 4-pyrradyl group, a 2-pyrradyl group, a 3-pyrradyl group, a 4-pyrradyl group, a 4-pyrradyl group, a 4-pyrradyl group, a 4-pyrradyl group, a 4-pyrradidyl group (a 3-byrriadidyl group) or a 4-pyrradidyl group, a 4-pyrradidyl group (a 2-flientyl group) a 4-pyrradidyl group, a 4-pyrradidyl group, a 4-pyrradidyl group or a 2-flientyl group, a 4-pyrradidyl group or a 2-flientyl group, a 4-pyrradidyl group or a 5-flientyl group, a 4-flientyl gr

[0030] The term '5- of 6-member non-aromatic heterocyclic group' used in the present specification refers to a monovalent group induced by removing 1 hydrogen atom from any position in a non-aromatic fing in which the number of atoms making up the ring is 5 or 6 and 1 or more hetero atoms are included in the atoms making up the ring. Specifically, examples of '5- or 6-member non-aromatic heterocyclic group' include a pyrroidinyl group, a tiperadyridinyl group, a terbaydroidinyl group, a terbaydroid group, a

[0031] The term "di C_{r.e.} alkylamino group" used in the present specification refers to a group in which 2 hydrogen atoms of the amino group are replaved with the "C_{r.e.} alkyl groups" defined above being the same as or different from each other. Specifically, examples of the term "di C_{r.e.} alkylamino group, a N. N-dim-thylamino group, a N, N-di-hydramino group, a N-m-butylamino group or the like, preferably a N, N-dimethylamino group, a N-m-butylamino group or the like, preferably a N, N-dimethylamino group, a N-m-butylamino group or the like, preferably a N, N-dimethylamino group, a N-m-butylamino group or the like.

[0032] The term "may have 1 or 2 substituents" used in the specification means that there may be 1 or 2 substituents in any combination in sites capable of substituting.

[0033] R¹ preferably represents a hydrogen atom, a halogen atom, an amino group, a $C_{1,6}$ alkyl group, a $C_{1,6}$ alkyl group, a $C_{1,6}$ alkyl group, and more preferably and hydrogen atom, an amino group or a $C_{1,6}$ alkyl group, and more preferably a hydrogen atom, an amino group or a $C_{1,6}$ alkyl group, with a methoxymethyl group being preferred as the $C_{1,6}$ alkoy $C_{1,6}$ alkyl group.

30 [0034] R² represents a hydrogen atom, an amino group or di C_{1.6} alkylamino group, with a hydrogen atom or an amino group being preferred.

[0035] One of X and Y is a nitrogen atom while the other is a nitrogen atom or an oxygen atom.

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[0036] The partial structure which contains X and Y and which is represented by formula (II) below:

has a structure such as those shown below, preferably with the left side bound to the 3-position of a pyridine ring via a single bond, and the right side bound to an Aring via a methylene group:

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100 [0037] In the case of the partial structure of formula (III), for example, the structure of the compound of the present invention is shown by the following formula:

$$R^1$$
 A Z R^3

[0038] It is preferable that one of X and Y be a nitrogen atom and the other be an oxygen atom, or that both X and Y be nitrogen atoms, and when one of X and Y is a nitrogen atom and the other is an oxygen atom, the partial structure which contains X and Y, and which is represented by the following formula (II):

has a structure such as that shown by formulae (III) or (IV) below, preferably with the left end bound to the 3-position of a pyridine ring via a single bond and the right end linked to an A ring via a methylene group:

while if X and Y are both nitrogen atoms, the partial structure which contains X and Y, and which is represented by the following formula (II):

has a structure such as that shown by formula (V) or (VI) below, preferably with the left end bound to the 3-position of a pyridine ring via a single bond and the right end bound to an A ring via a methylene group:

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[0039] A ring A represents a 5- or 6-member heteroary ring or a benzene ring which may have a halogen atom or 1 or 2 Or., a kly groups, and preferably represents a pyridine ring, a benzene ring, a lutran ring, a thiophener ring or a pyrrole ring, or more preferably a pyridine ring, a benzene ring, or a benzene ring.

[0040] Z preferably represents a single bond, a methylene group, an ethylene group, an oxygen atom, a sulfur atom, -OH₂O-, -OOH₂-, -NIH-, -NHOH₂-, -OH₂N-, or -SOH₂-. Of these a methylene group, an oxygen atom, -OH₂O- or -OOH₂- is preferred, and an oxygen atom, -OH₂O- or -OOH₂- is persered, and an oxygen atom, -OH₂O- or -OOH₂- is persered and oxygen atom, -OH₂O- or -OOH₂- is persered and oxygen atom, -OH₂O- or -OOH₂- is persered and oxygen atom, -OH₂O- or -OOH₂- is persered, and oxygen atom, -OH₂O- or -OOH₂- is persered and oxygen atom, -OH₂- is persered and -OH₂- is persered and -OH₂- is persered and -OH₂- is persered and -OH₂- is persere

[0041] $^{\rm RJ}$ represents a hydrogen atom, halogen atom, a $^{\rm C}_{1.6}$ alkyl group, a $^{\rm C}_{2.8}$ cycloalkyl group, a $^{\rm C}_{6.10}$ anyl group or a 5 - or 8-member ring heteroaryl group which may have 1 or 2 substituents each selected from substituent group α : substituent froup α 1

a halogen atom, a cyano group, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group, C₁₋₆ alkoxycarbonyl group, a C₃₋₈ cycloalkyl group, a C₃₋₈ alkenyl group and a C₃₋₈ alkynyl group.

[0042] Examples of preferable groups as R³ include an -butly (group, a cyclopropy) group, a phenyl group, a fluorophenyl group, a furyl group, a chiorofunyl group, a methyltini group, a thienyl group, a promothienyl group, a methyltinienyl group, a pyridyl group and a methyltypridyl group, more preferably a n-butlyl group, a cyclopropyl group, a phenyl group, a fluorophenyl group, a pyridyl group are methyltypridyl group.

25 [0043] Z and R³ may constitute the substituent of ring A in any combination. Preferable examples of R^{3,2} -as the substituent of ring A constituted in this way include a phenoxy group, a benzydoxy group, a 2-fluoro-benzyloxy group, a 4-fluoro-benzyloxy group, a pyridin-2-yloxymethyl group, a 6-methyl-pyridin-2-yloxymethyl group, a 6-methyl-pyridin-2-yloxymethyl group, a 4-methyl-pyridin-2-yloxymethyl group, a 4-methyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymethyl-pyridin-2-yloxymeth

39 [0044] Preferable examples of the compounds of the present invention include the following compounds:

- 3-(3-(4-benzyloxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;
- 3-(3-(4-(pyridin-2-vloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-vlamine:
- 3-(3-(4-(pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;
- 3-(3-(4-(4-methyl-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;
 - 3-(3-(6-benzyloxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine;
 - 3-(3-(4-benzyloxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
 - 3-(3-(4-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridine-2,6-diamine;
- 3-(3-(4-(6-methyl-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
- 40 3-(3-(4-butoxymethyl-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
 - 3-(3-(4-phenoxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
 - 3-(3-(4-(4-methyl-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
 - 3-(3-(6-benzyloxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
 - 6-methoxymethyl-3-(3-(4-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine; 3-(5-(4-benzyloxy-benzyl)-isoxazol-3-yl)-pyridin-2-ylamine;
 - 3-(5-(4-(pyridin-2-yloxymethyl)-benzyl)-isoxazol-3-yl)-pyridin-2-ylamine;
 - 3-(1-(4-benzyloxy-benzy)-1H-pyrazol-4-yl)-pyridin-2-ylamine;
 - 3-(1-(4-(pyridin-2-yloxymethyl)-benzyl)-1H-pyrazol-4-yl)-pyridin-2-ylamine;
 - 3-(1-(4-butoxymethyl-benzyl)-1H-pyrazol-4-yl)-pyridin-2-ylamine;
 - 3-(1-(4-benzyloxy-benzyl)-1*H*-pyrazol-4-yl)-pyridin-2,6-diamine; 3-(1-(4-(pyridin-2-yloxymethyl)-benzyl)-1*H*-pyrazol-4-yl)-pyridin-2,6-diamine;
 - 3-(1-(4-butoxymethyl-benzyl)-1H-pyrazol-4-yl)-pyridin-2,6-diamine;
 - 3-(3-(6-phenoxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
 - 3-(3-(4-(5-fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;
 - 3-(3-(4-(4-methyl-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine:
 - 3-(3-(4-(6-fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;
 - 3-(3-(4-(4-chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;
 - 3-(3-(4-(6-chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;

- 3-(3-(6-phenoxymethyl-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine;
- 3-(3-(4-(6-fluoro-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;
- 3-(3-(6-(4-fluoro-benzyloxy)-pyridin-3-vlmethyl)-isoxazol-5-vl)-pyridin-2-vlamine:
- 3-(3-(4-(5-chloro-furan-2-vlmethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-vlamine:
- 5 3-(3-(4-phenylaminomethyl-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;

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- 3-(3-(4-(4-methyl-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
- 3-(3-(4-(6-fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
- 3-(3-(4-(5-methyl-furan-2-ylmethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
- 3-(3-(4-(4-chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
- 3-(3-(4-(6-chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
- 3-(3-(6-phenoxymethyl-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2.6-diamine:
- 3-(3-(4-(5-fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
- 3-(3-(4-(6-fluoro-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine; 3-(3-(1-benzyl-1H-pyrrol-3-ylmethyl)-isoxazol-5-yl)- pyridin-2,6-diamine;
- 3-(3-(6-(4-fluoro-benzyloxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
- - 3-(3-(4-(5-chloro-furan-2-ylmethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
 - 3-(3-(6-(3-fluoro-phenoxy)pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
 - 3-(3-(4-phenylaminomethyl-benzyl)-isoxazol-5-yl)-pyridin-2.6-diamine: 3-(3-(6-(4-fluoro-phenoxy)-pyridin-3-vimethyl)-isoxazol-5-vl)-pyridin-2.6-diamine:
- 3-(3-(4-(thiazol-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine;
 - 3-(3-(5-(4-fluoro-phenoxy-thiophen-2-vlmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine: 6-methoxymethyl-3-(3-(4-(pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;
 - 6-methyl-3-(3-(4-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;
 - 5-(3-(4-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine;
- 25 3-(1-(4-(pyridin-2-ylmethoxy)-benzyl)-1 H-pyrazol-4-yl)-pyridin-2-ylamine; and
 - 3-(3-(4-(pyridin-2-vloxymethyl)-benzyl)-isoxazol-5-vl)-pyridine.

[0045] Examples of the term "salt" used in the present specification include a salt with an inorganic acid, a salt with an organic acid, a salt with an acidic amino acid or the like. Among these salts, it is preferable that a salt used herein be a pharmaceutically acceptable.

[0046] Preferable examples of the sait with the inorganic acid include saits with hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid or the like. Preferable examples of the salt with the organic acid include salts with acetic acid, succinic acid, furnaric acid, maleic acid, tartaric acid, citric acid, lactic acid, stearic acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid or the like.

- [0047] Preferable examples of the salt with the acidic amino acid include salts with aspartic acid, glutamic acid or the like. Preferable examples of the salt with the basic amino acid include salts with arginine, lysine, ornithine or the like, [0048] The term "antifungal agent" used in the present specification refers to a preventive agent or a the rapeutic agent for fungal infection.
- [0049] The compounds according to the present invention, or salts or hydrates thereof, can be formulated into tablets, powders, fine granules, granules, coated tablets, capsulates, syrups, troches, inhalants, suppositories, injections, ointments, eye cintments, tapes, eye drops, nose drops, ear drops, cataplasms, lotions or the like, by the conventional

[0050] Such formulation can be achieved by using typical diluents, binders, lubricants, colorants, flavorants, and, as necessary, stabilizers, emulsifiers, absorbefacients, surfactants, pH modulators, preservatives, antioxidants or the like, and materials commonly used as ingredients of pharmaceutical preparations according to the conventional methods. For example, an oral preparation can be produced by combining a compound of the present invention or a pharmaceutically acceptable salt thereof with a diluent, and if required, a binder, a disintegrating agent, a lubricant, a colorant, a flavorant or the like, and formulating the mixture into powders, fine granules, granules, tablets, coated tablets, capsules or the like according to the conventional methods.

[0051] Examples of the materials include animal and vegetable oils such as soy bean oil, beef tallow, and synthetic glyceride; hydrocarbons such as liquid paraffin, squalane, and solid paraffin; ester oils such as octyldodecyl myristate and iso-propyl myristate; higher alcohols such as cetostearyl alcohol and behenyl alcohol; silicone resins; silicone oils; surfactants such as polyoxyethylene fatty acids ester, sorbitan fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene hydrogenated castor oil, and polyoxyethylene polyoxypropylene block co-polymer; water-soluble polymers such as hydroxyethyl cellulose, polyacrylic acid, carboxyvinyl polymer, polyethylene glycol, polyvinylpyrrolidone, and methyti cellulose; lower alcohols such as ethanol and isopropanol; polyhydric alcohols such as glycerol, propylene glycol, dipropylene glycol, and sorbitol; sugars such as glucose and sucrose; inorganic powder such as anhydrous silicic acid, magnesium aluminum silicate, and aluminum silicate; and pure water. Examples of the diluents include lactose,

corn starch, white sugar, glucose, mannitol, sorbitol, crystalline cellulose, silicon dioxide or the like. Examples of the binders include polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, gum Arabic, tragacanth, gelatin, shellac, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polygropylene glycol-polyoxyethylene block co-polymer, and meglumine or the like. Examples of disintegrating agents include starch, agar, gelatin powder. crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin, pectin, calcium carboxymethyl cellulose or the like. Examples of lubricants include magnesium stearate, take, polyethylene glycol, silica, hydrogenated vegetable oil or the like. Examples of colorants include those pharmaceutically acceptable. Examples of flavorants include cocoa powder, peppermint camphor, aromatic powder peppermint oil, Borneo camphor, cinnamon powder or the like. Tablets and granules may be coated with sugar, or if required, other appropriate coatings can be made. Solutions, such as syrups or injectable preparations, to be administered can be formulated by combining a compound according to the present invention or a pharmaceutically acceptable salt thereof with a pH modulator, a solubilizing agent, an isotonizing agent or the like, and if required, with an auxiliary solubilizing agent, a stabilizer or the like, according to the conventional methods. Methods for manufacturing external preparations are not limited and such preparations can be manufactured by the conventional methods. Specifically, various materials typically used for manufacturing pharmaceu-15 ticals, quasi drugs, cosmetics or the like can be used as base materials for the external formulation. More specifically, examples of base materials to be used include animal and vegetable oils, minerals oils, ester oils, wax, higher alcohols, fatty acids, silicone oil, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals, pure water or the like. Furthermore, external preparations of the present invention can contain, as required, pH modulators. antipolidants, chelating agents, antibacteria/antifungal agents, colorants, odoriferous substances or the like. But this does not limit the type of base materials that are to be used in the external preparations of the present invention. If required, the preparation may contain differentiation inducers, blood flow improving agents, antimicrobial agents, antiphologistics, cell activators, vitamins, amino acids, humectants, keratolytic agents or the like. The amount of the base materials listed above is adjusted within a concentration range used for producing typical external preparations.

[0052] When administering the compound of the present invention or a salt thereof, the forms of the compounds are not limited in particular, and the compound can be given orally or parenterally by the conventional method. For instance, the compound can be administered as a dosage form such as tablets, powders, granules, capsules, syrups, troches, inhalants, suppositories, injections, ointments, eye ointments, tapes, eye drops, nasal drops, ear drops, catapiasms and informs.

[0053] Dose of a medicament according to the present invention can be selected appropriately according to symptom severity, age, sex, body weight, forms of administration, type of salts, specific type of disease or the like.

[0054] The does varies remarkably depending on the patient's disease, symptom severity, age and sex, drug susceptibility or the like. An oral preparation according to the present invention can be generally administered once or several time at a does of from 1 to 1000 mg/adult/day, preferably from 10 to 2000 mg/adult/day. An injection according to the present invention can be generally administered at a does of from 0.1 to 10000 mg/adult/day, preferably from 1 to 2000 mg/adult/day.

[General synthesis methods]

[0055] The method for manufacturing the compounds represented by formula (i) according to the present invention (treninafter referred to as compounds (ii)) is discussed here. The compounds according to the present invention can be synthesized by ordinary organic synthesises methods, but for example, among the compounds (ii), the compounds represented by formula (1a), formula (2a), formula (3a), formula (3

[Manufacturing Method 1] Typical method for manufacturing compound (1a):

50 [0056]

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(wherein ring A, R1, R2, R3, and R4 and Z are defined as above.)

[Manufacturing Method 1-1] Method for manufacturing compound (1 a):

[0057]

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$$(1p) \qquad (1a) \qquad (1a)$$

$$K_1 \longrightarrow K_2 \longrightarrow K_3 \longrightarrow K_4 \longrightarrow K_5 \longrightarrow K$$

(wherein the ring A, R1, R2, R3, and Z have the same meanings as defined above.)

[0058] Compound (1 b) which is a commercially available product can be used as is or compound (1 b) can so be manufactured from a commercially available product by the well known methods. In addition, compound (1 b) can be manufactured by the methods described in the Manufacturing Examples in the Examples or according to [Manufacturing Method 1-2:1 for the like.

[0059] Compound (1 c) can be manufactured by the well known methods from a commercial available product. Compound (1 c) can also be manufactured by the methods described in the Manufacturing Examples in the Examples or according to [Manufacturing Method 1-3-1] and the like.

[Step 1]

[0060] This step is a step wherein compound (1 a) is obtained by reacting compound (1b) and compound (1c) in the presence of a base. There are no particular imitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include either solvents such as littrahydroturan and dethyl either, aromatic hydrocarbon solvents uch as benzane and toluener, amide solvents such as IN-Memethylformamide and N-methylgymoridinoner; alcohol solvents such as methanol and ethanoi; and water, methylene chloride, chloroform, ethyl sectats, dimethyl sulfoxide, mixed solvents of the foregoing and the like. Exemples of the base used in this reaction include tierburyanine, IN-Meisogropylethylamine, soldum bydrogencarbonate, potassium carbonate and the like. Compound (1c) can be used in the amount of 1 to 3 equivalents, perferably 1 to 2 equivalents, based on compound (1c). The base can be used in the amount of 1 to 3 equivalents based on compound (1c). The reaction temperature is from noom temperature to reflux temperature, and the reaction time is from 10 minuses to 24 hours.

[Manufacturing Method 1-2-1] Method 1 for manufacturing compound (1b):

[0061]

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(wherein R¹ and R² are defined as above, Hal represents a halogen atom, and R⁵ and R⁶ represent each independently C₁ alkyl groups.)

[0062] Compound (1b-1) which is a commercially available product can be used as is, or compound (1 b-1) can also be manufactured from commercially available products by the well known methods.

[Step 1-1]

[0063] This step is a step wherein compound (1 b-2) is obtained by reacting compound (1b-1) with an ethynyl silane derivative. Compound (1b-2) can be obtained by reacting compound (1b-1) with an ethynyl sllane derivative in the presence of a palladium catalyst, a base and a copper catalyst. A phosphine ligand may also be added to obtain good results. There are no particular limitations on the solvent used in this reaction as long as it can dissolve the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include ether solvents such as tetrahydrofuran and 1,4-dioxane; amide solvents such as N,N-dimethylformamide and N-methylpyrrolidinone; and acetonitrile, dimethyl sulfoxide, mixed solvents of the foregoing and the like. Examples of the ethynyl silane derivative include trimethylsilylacetylene, triethylsilylacetylene, triisopropylsilylacetylene, t-butyldimethylsilylacetylene and the like. Examples of the palladium catalysts include palladium (II) acetate, tetrakis(triphenylphosphine)palladium (0), dichlorobis(triphenylphosphine)palladium (II), dichlorobis(tri-o-tolylphosphine)palladium (II), bis(tri-i-butylphosphine) palladium (0), or tris(dibenzylideneacetone)dipalladium (0) and the like. Examples of the base include triethylamine, N, N-diisopropylethylamine, pyridine and the like. Examples of the phosphine ligand include triphenylphosphine, tri-o-tolylphosphine, tri-t butylphosphine and the like. A copper catalyst can be added in this reaction. Examples of the copper catalyst include copper, copper (I) iodide, copper (I) bromide, copper (I) chloride and the like. The ethynyl silane derivative is used in the amount of 1 to 5 equivalents based on compound (1 b-1). The palladium catalyst is used in the amount of 0.01 to 0.3 equivalents based on compound (1 b-1). The base is used in the amount of 2 to 5 equivalents based on compound (1b-1). The phosphine ligand is used in the amount of 0.01 to 1.2 equivalents based on compound (1b-1). The copper catalyst is used in the amount of 0.001 to 0.3 equivalents based on compound (1 b-1). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 30 minutes to 24 hours,

[Step 1-2]

[0064] This step is a step wherein compound (1b) is obtained by reacting compound (1b-2) with a base. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents in this step include their solvents such as tetrahydrofuran and diethyl ether; alcohol solvents such as methanol and ethanol; amide solvents such as NN-dimethylformanide and N-methylpyrrolidinone; and accitoritifie, dimethyl sulfoxide, water, mixed solvents of the foregoing and the like. Examples of the base include potassium carbonate, sodium hydroxide, tetrabutylammonium fluoride, potassium fluoride, cesium fluoride and the like. The base is used in the amount of 0.05 to 10 equivalent based on compound (1b-2). The reaction temperature is from 0°C to reflux temperature; and the reaction time is from 5°C to reflux temperature; and the reaction time is from 5°C to reflux temperature; and the reaction time is from 5°C to reflux temperature; and the reaction time is from 5°C to reflux temperature; and the reaction time is from 5°C to reflux temperature; and the reaction time is from 5°C to reflux temperature; and the reaction time is from 5°C to reflux temperature; and the reaction time is from 5°C to reflux temperature; and the reaction time is from 5°C to reflux temperature; and the reaction time is from 5°C to reflux to 24 hours.

[Manufacturing Method 1-2-2] Method 2 for manufacturing compound (1 b):

[0065]

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(wherein R1 and R2 are defined as above, and R7 represents a C1.6 alkyl group.)

[0066] Compound (1 b-3) which is a commercially available product can be used as is, or compound (1 b-3) can also be manufactured from commercially available products by the well known methods.

[Step 1-3]

[0067] This step is a step wherein compound (I b-4) is obtained by seterifying compound (I b-3) in the presence of an acid. The solvent used in this reaction is preferably an alcohol solvent such as methanol, ethanol and the like. Examples of the acids include sulfuric acid, hydrochloric acid, hydrobromic acid and the like. The acid can be used in the amount from a catalytic amount to a solvent amount based on compound (I b-3). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 1 hour to 72 hours.

[0068] Compound (1 b-4) can also be obtained from compound (1 b-4) by the methods described as Alternative Methods (1), (2) and (3) below.

10 [0089] Alternative Method (1): Compound (1 b-4) can be converted into a methyl ester derivative using diazomethane or trimethylsily diazomethane. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent used in this reaction include either solvents such as tetrainydrofuran and diethyl either, aromatic hydrocarbon solvents such as benzene and toluener; alcohol solvents such as methanol and ethanol; and methylene chloride, hexane, mixed solvents of the foregoing and the like. The diazomethane or trimethylelyl diazomethane is used in the amount of 1 to 2 equivalents based on compound (1 b-3). The reaction temperature is from 0°C to room temperature, and the reaction time is from 10 minutes to 24 hours.

[0070]. Alternative Method (2): Compound (1b-3) can be converted into compound (1b-4) using an alkylating agent in the presence of a base. There are no particular limitations on the solvent used in this reaction as long as it disolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include either solvents such as the hydroduran and diethyl either, aromatic hydrocarbon solvents such as benzene and toluence; mide solvents such as the NA indirectly instruction and A-methylyprointilionica; alcohol solvents such as methanol and ethanol; and water, acetone, acetomic, dimethyl sulfoxide, mixed solvents of the foregoing and the like. A phase-transfer catalyst such as terhabulyalmomium bromitic can also be added to this reaction. Examples of the base used in this reaction include potassium hydroxide, sodium hydroxide, lithium hydroxide, potassium carbonate, ceslum carbonate, ceslum fluoride and the like. The amount of 1 to 1.5 equivalents based on compound (1b-3). The alkylating agent is used in the amount of 1 to 2 equivalents based on compound (1b-3). The reaction temperature is from 0°C to reflux temperature, and the reaction intens is from 1 hour 27 brours.

30 [0071] Alternative Method (3): Compound (1 b-3) can be convented into an acid chloride using a halogenating agent, and then converted into compound (1 b-4) to addition of alcohol. There are no particular imitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include aromatic hydrocarbon solvents such as becare an antiolusine; amide solvents such as N.N-dimethylformamide and N-methylgymolidinone; and acetonitrile, methylene chloride, 1,2-dichlorochane, mixed solvents of the foregoing and the like. The halogenating agent can also be used as the solvent. A catalytic amount of prydrine or a phase-transfer catalyst such as benyt/tetritylammonium chinorice can also be added to this reaction. Examples of the halogenating agent is beared in the amount of 1 to 20 equivalents abortion include methanol, ethanol and the like. The halogenating agent is used in the amount of 1 to 20 equivalents based on compound (1 b-3). The alcohol is used in the amount of 1 to 20 equivalents are considered and the solution of the control of the control of the care of the care of the control of the control of the control of the care o

[Step 1-4]

[0072] This step is a step wherein compound (1 b-5) is obtained by reduction of compound (1b-4). There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain scatch without impeding the reaction, but tetrahydrofuran is preferred. Examples of the reducing agent in this reaction include lithium aluminum hydride, aluminum chloride in the amount of 1 to 1.5 equivalents based on lithium aluminum hydride, lithium borohydride and the like. The reducing agent is used in the amount of 0.5 to 4 equivalents based on compound (1b+3). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10°C to reflux temperature.

[Step 1-5]

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[0073] This step is a step wherein compound (1 b-6) is obtained by oxidation of compound (1 b-5). There are no

particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Exemples of the solvents used in this reaction include either solvents such as tetrahydro-furan and diethyl ether, aromatic hydrocarbon solvents such as benzene and toluone; alcohol solvents such as methanol and ethanol; and methylene chloride, acetone, hexane, mixed-solvents of the foregoing and the like. Examples of oxidizing agent used in this reaction include manganese dioxide, pyridinium chloronate, dimethyl sulfoxide - activator, tetrapropharmonium perruthenate, dichlorotristriphenylphosphine/puthenium (il), 1,1;1-tris(acety-toly-1,1-dimylor-1) 2-benziodoxo/3-4(H)-on (Dess Ahrin Periodinana) and the like. The oxidizing agent is used in the amount of from the catalytic amount to 20 equivalents based on compound (1 b-5). When oxidizing with dimethyl sulfoxide activator, examples of the activator include acid anhydrides such as acetic anhydride and trifluoroacetic anhydride; acid chlorides is used in the amount of 1 to 20 equivalents based on the activator. When using tetaprocyl ammonium peruthenate or dichloroids (tiphenylphosphine)rulnelmul (ii) in a catalytic amount, an oxidizing agent such as N-methylmorpholine-N-oxide or bist(trimethylsily)peroxide can be used at the same time. The reaction temperature is from -78°C to reflux temperature, and the reaction time is from 10 minutes to 27 hours.

[Step 1-6]

10074] This step is a step wherein compound (1 b) is obtained from compound (1 b-0) in the presence of a base using a cliazo compound. Examples of the disezo compound used in this reaction include trimstylely diszonethere, (1-diszo-2-cooppoyly-phosphoric acid dimethyl ester, diszonethyl phosphoric acid dimethyl ester in the tike. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include other solvents such as strainly-different and delityly ether, aromatic hydrocarbon solvents such as benzane and toluser, aboth los olvents such as methanol and exhancis, and methylane chloride, hexane, mixed solvents of the oregoing and the like. When using if methylayily diazomethane as the diazo compound, n-buyl lithium and lithium discorpoylamide can be used as the base. When using a phosphoric acid destre derivative such as (1-diazo-2-cooppoyly)-phosphoric acid dimethyl seter as the diazo compound, potassium carbonate, potassium butoxide and the like can be used as the base. The diazo compound is used in the amount of 1 to 1.5 equivalents based on compound (10-6). The reaction temperature is from -78°C to room temperature, and the reaction time is from 1 on injuries to 2.4 horn, and the reaction time is from 1 on injuries to 2.4 horn, and the reaction time is from 1 on injuries to 2.4 horn, and the reaction time is from 1 on injuries to 2.4 horn, and the reaction temperature is from -78°C to room temperature, and the reaction time is from 1 on injuries to 2.4 horn, and the reaction interest to 2.4 horn, and the reaction interest to 2.4 horn, and the reaction time is from 1 to 1 mixes to 2.4 horn, and the reaction temperature is from -78°C to room temperature, and the reaction time is from 1 to 1 mixes to 2.4 horn, and the reaction in the proposition of the propositio

[0075] Compound (1 b) can also be obtained from compound (1 b-6) by the methods given below as Alternative Methods (1).

[0076] Alternative Method (1): Compound (1 b-6) can be converted into a dihaloalkene in the presence of a base, and then reacted with a base to obtain compound (1b).

35 [0077] Dihaloalkene synthesis: There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent used in this synthesis include ether solvents such as tetrahydrofuran and diethyl ether; aromatic hydrocarbon solvents such as benzene and toluene; and hexane, mixed solvents of the foregoing and the like. Examples of the resgent for converting compound (1 b-5) into dihaloalkene include (clichormathlyl-phosphoric acid dimethyl eater, dibromemethyl tribneyl) phosphonium bromide (Tetrahedron Letters, Vol. 40, No.49, 8575-8578) and the like. Examples of the base in this reaction include lithium disopropylamide, potassium Foutoxide and the like. The reagent for converting into dihaloalkene is used in the amount of 1 to 2 equivalents based on compound (1 b-6). The base is used in the mount of 1 to 2 equivalents based on compound (1 b-6). The reaction temperature is from -78°C to room temperature, and the reaction time is from 1 minutes to 24 hours.

[0078] As another synthetic method of dihaloalkene, following alternative method using carbon tetrabromicis can be applied. Compound (1 b-0) is conviered into dihaloalkene, by reacting adnote hetrabromicis and triphenylphosphine. Zinc can also be added in this reaction. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Preferable examples of the solvent used in this synthesis include tetrahydrofuran and methylene chloride. The carbon tetrahromide is used in the amount of 1 to 2 equivalents based on compound (1 b-8). The triphenylphosphine is used in the amount of 2 to 4 equivalents based on compound (1 b-8). The zinc is used in the amount of 1 equivalent based on the carbon tetrahromide. The reaction temperature is from 0°C to room temperature, and the reaction time is from 10 minutes to 12 hours.

[0079] Synthesis of compound (1 b) from dihaloalkene: There are no particular limitations on the solvent used in this reaction as long as it fassioves the starting materials to a certain extent without impeding the reaction. Examples of the solvent used in this synthesis include either solvents such as terrahyrdrofuran and delithyl ether; aromatic hydrocarbon solvents such as benzene and toluene; and hexane, mixed solvents of the foregoing and the like. Examples of the base used in this reaction include n-buryl lithium, *buryl filthium, potassium *buroxide* and the like. The base is used in the amount of 2 to 3 euluviaents based on the difficultiene. The reaction the protection the protection of the promise of the protection of the protecti

and the reaction time is from 10 minutes to 24 hours.

[Manufacturing Method 1-2-3] Method for manufacturing compound (1 b-3):

5 [0080]

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15 (wherein R² and Hal are defined as above, and R⁸ represents a C₁₋₆ alkyl.)

[0081] Compound (1 b-7) which is a commercially available product can be used as is, or compound (1 b-7) can also be manufactured by from a commercially available product with the well known methods, for example, WO 2005/033079 A1, pp 88-86, etc.

Step 1-7]

[0082] This stap is a step wherein compound (1 b-9) is obtained by reacting compound (1b-7) with an alcohol in the presence of a base. This step is certifed out according to the procedures of (Step 1-39) given below or the method disclosed in Journal of Medicinal Chemistry, Vol. 48, No. 5, pp 702-705 or the like. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Exemples of the solvents in this step include either solvents such as tetrahydroutna and dettyle their, aromatic hydrocarbon solvents such as benzane and toluene; amide solvents such as INI-dimethyformamide and N-methylpy-roidinone; alcohol solvents such as methanol and effect, substance, and mischly subdickle, mixed solvents of the recepting and the like. Exemples of the base in this step include sodium hydride, potassium (butoxide, potassium hearmethy/disilazide and the like. A copper catalyst can be added in this reaction. Exemples of the copper catalyst can be added in this reaction. Exemples of the copper catalyst can be added in this reaction. Exemples of the copper catalyst can be added in this reaction. Exemples of the copper catalyst can be added in this reaction. Exemples of the copper catalyst can of the solvent and the like. A test of the copper catalyst can be added in this reaction. Exemples of the copper catalyst can of the solvent and the like. The base can be used in the amount of 1 to 20 equivalents based on compound (1 b-7). The copper catalyst can be used in the amount of the reaction time is form 30 mixets be 48 hours.

[Manufacturing Method 1-2-4] Method 1 for manufacturing compound (1b-4):

[0083]

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(wherein R2, R7 and Hal are defined as above and R9 represents a C1.6 alkyl group.)

[0084] Compound (1 b-9) which is a commercially available product can be used as is, or compound (1b-9) can also be manufacture from commercially available products by the well known methods. Compound (1b-9) which is a commercially available product can be used as is, or compound (1b-9-1) can also be manufactured from commercially available products by the well known methods (for example, WC 2006/033079 AI, pp 85-86, etc.).

[Step 1-8]

[0085] This step is a step wherein compound (1b-10) is obtained by reacting compound (1 b-9) with compound (1b-

9-1) in the presence of a palladium catalyst. A phosphine Igand may also be added to obtain good results. There are no particular limitations on the solvent used in this reaction as long as it discolves the starting materials to a certain content without impeding the reaction. Examples of the solvents in this etsp include either solvents such as 1.4-doxame and tetrally/dofuran; aromatic hydrocarbon solvents such as 1.0-doxame and tetrally/dofuran; aromatic hydrocarbon solvents such as 1.0-doxame and tetrally/dofuran; aromatic hydrocarbon solvents such as 1.0-doxame of the palladium catalyst include palladium (il) decirate, his/dibancy/ildenexectione-ligiballadium (ii), Carbiorobis(hipheny)-hosphinoplaladium (iii), discribering-plandium (iii), bis(hir-buty/phosphinoplaladium (iii), training-phosphinoplaladium (iii), training-phosphinoplaladium (iii), and the phosphinoplaladium (iii), and the phosphinoplaladium (iii), and the phosphinoplaladium (iii) and the phosphinoplaladium (iii), and the phosphinoplaladium (iii), and the phosphinoplaladium (iii) and the phosphinoplaladium (iiii) and the phosphinoplaladium (iiii) and the phosphinoplalad

[Manufacturing Method 1-2-5] Method 2 for manufacturing compound (1b-4)

[0086]

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(wherein Hai, R^2 and R^7 are defined as above, R^{10} and R^{11} each independently represents C_{1-6} alkyl groups.) [0087] Compound (1b-9) and compound (1b-9-2) which are commercially available products can be used as is or may be obtained from commercially available or other by the known methods

[Step 1-9]

[0088] This step is a step wherein compound (1b-11) is obtained by alkylating compound (1 b-9) through a reaction with compound (1 b-92) in the presence of a palladium catalyst. Compound (1 b-11) can be manufactured according to the method of similar to those of [Step 1-8].

[Manufacturing Method 1-2-6] Method for manufacturing compound (1 b-5)

[0089]

(wherein R1 and R2 are defined as above.)

[0090] Compound (1 b-3) which is a commercially available product can be used as is or may be obtained from commercially available products by the known methods.

[Step 1-10]

55 [0091] This step is a step wherein compound (1 b-5) is obtained by reducing compound (1b-3). Compound (1 b-5) can be manufactured according to methods similar to those of [Step 1-4].

[Manufacturing Method 1-2-7] Method for manufacturing halogen-modified product of pyridine ring

[0092]

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(wherein R1, R2 and Hat is defined as above; R12 represents a hydrogen atom, a hydroxy group, or OR7 (R7 is defined as above).)

[0093] Compound (1b-12) which is a commercially available product can used as is or may be obtained from commercially available products by the known methods.

[Step 1-11]

[0094] This step is a step wherein compound (1b-13) is obtained by substituting a halogen atom for a hydrogen atom on the pyridine ring of compound (b t-12). This step can be carried out according to, br instance, European-Journal of Medicinal Chemistry, Vol.12, No.6, 531-536, or, Journal of Organic Chemistry, Vol.49, No.26, 5237-5243, or the like. There are no particular initiations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Exemples of the solvent include halogen solvents such as tarriding and chemistry of the solvent include halogen solvents such as chrodrom and dichloromethane; either solvents such as tetrahydrofuran and diethyle there; amide solvents such as N.N-dimethylformatide and N-methylpryroridinone, acid solvents such as a sectic acid and hydrochoric acid aqueous solvitoris, dimethyl sulfoxide; castonitrile; nixed solvents of the foregoing, or the like. Exemples of halogenation reagent include N-chiorosculchinide, N-bromosculchinide, N-bromosculchinide, N-bromosculchinide, N-bromosculchinide, N-chiore and bromoline. The halogenation reagent is used in the amount of 1,0 to 1.5 equivalents based on compound (1b-12). The reaction temperature is from room temperature to 50°C, and the reaction time is from 5 minutes to 24 hours.

[Manufacturing Method 1-2-8] Method for manufacturing compound (1 b-6)

[0095]

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(wherein R2 and R7 is defined as above.)

[0096] Compound (1 b-14) can be manufactured according to the methods described in [Manufacturing Method 1-2-4] given above.

[Step 1-12]

50 [0097] This step is a step wherein compound (1 b-15) is obtained by reducing compound (1b-14). Compound (1b-15) can be manufactured according to the methods similar to those of [Step 1-4].

[Step 1-13]

55 [0098] This step is a step wherein compound (1b-16) is obtained by oxidizing compound (1b-15). Compound (1b-16) can be manufactured according to the methods similar to those of [Step 1-5].

[Step 1-14]

[0993] This stop is a step wherein compound (1b-17) is obtained by reacting compound (1b-18) with boron tribromics. There are no particular limitations on the solvent used in this reaction is along as it discoves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include halogenated hydrocarbon solvents such as methylene chloride; aromatic hydrocarbon solvents such as benzene and fubuser; mixed solvents of the foregoing, or the like. Boron ribromide can be used in the amount of 1 to 5 equivalents based on compound (1b-16), referably 3 equivalents. The reaction temperature is from -20°C to room temperature, and preferably 0°C. The reaction time is 10 minutes to 24 hours.

[Manufacturing Method 1-3-1] Method 1 for manufacturing compound (1c):

[0100]

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(wherein ring A, R³, Z and Hal are defined as above, R¹³ and R¹³ represent C₁_e alkyl groups or crosslinked -(CH₂)_e, n is 2 c r³, and R¹⁴ represents a hydrogen atom, a sodium atom, a potassium atom and a lithium atom.) [0101] Each compound in the above reaction scheme which is commercially autilable products and be used as is, or each compound can also be manufactured from commercially available products by the well known methods. In addition, each compound can be manufactured from commercially available products by the well known methods. In addition, each compound can be manufactured by the methods described in the manufacturing examples in the examples and by the methods described in [Manufacturing Method 1-3-210].

[Step 1-15]

[0102] This step is a step wherein compound (1.6.1) is obtained by reacting a formytation reagent with an organometatine compound obtained by substituting a metal atom for the halogen atom in compound (1.6.1). There are no perticular imitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Preferable examples of the solvents used in this reaction include their solvents such as tealing orduran and deliry effer. Examples of the organometalis compound include organoithium compounds obtained using a base such as n-buly lithium, a buly lithium him, abuly lithium and lithium disopropylamide, or Grignard reagents obtained using a base such as n-buly lithium, a buly lithium, a buly lithium bromide and slopropylimageisum inclinde. A catalytic amount of lodine, distornmental and the like can be added when preparing the Grignard reagents using metal rangersium. The temperature for preparing the organoil/him compound is from .78°C to from temperature, preferably from .78°C to .40°C, the base is used in the amount of 1 to 1.5 equivalents based on compound (1.6.1), and the reaction time is from from temperature to reflux temperature for preparing the Grignard reagents using metal magnesium is from room temperature to reflux temperature for the solvent, the metal magnesium is used in the amount of 1 to 2 equivalents based on compound (1.6.1), and the reaction time is from 3 minutes to 2.4 hours. The temperature for preparing the Grignard conception (1.6.1), and the reaction time is from 30 minutes to 2.4 hours. The temperature for preparing the Grignard reagents using eithy magnesium bromide or isopropyl magnesium bromut of 1 to 1.6 or efflux temperature, the ethyl magnesium bromide or isopropyl magnesium bromut of 1 to 1.6 or efflux temperature.

(1c-1), and the reaction time is from 5 minutes to 12 hours. Examples of the formylation agents include dimetryformamine, N-formylpiperidine, N-formylmorpholine, N-methylformamilide and the like. The formylation reagent can be used in the amount of 1 to 20 equivalents, preferably 1 to 2 equivalents, based on the organometallic compound. The temperature for reacting the organometallic compound and formylation reagent is from -78°C to room temperature in the case of the organolithium compounds, with a reaction time being from 5 minutes to bours, while in the case of the 6ngard reagents the reaction temperature is from -78°C to reflux temperature of the solvent, with a reaction time being from 5 minutes to 724 hours.

[Step 1-16]

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[0103] This stop is a stop wherein compound (1c-6) is obtained by reacting an acid to the acetal of compound (1c-2), so as to deprotect the acetal. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent used in this reaction include ether solvents such as tetrahydrofuran and diethyl ether; aromatic hydrocarbon solvents such as benzene and toluens; armide solvents such as N-M-dimethyl/mormalide and N-methylypyrrollinone; alcohol solvents such as methanol and ethanol; dimethyl sulfoxide and water, mixed solvents of the foregoing and the like. Examples of the acid in this reaction include inorganic acids such as a hydrochoric acid, sulfuric acid, and hydrotromic acid; organic acids such as citific acid, trifluroreactic soci, proteonessultion local dant the like. The acid can be used in the amount of from a catalytic acid, and the social proteoness amount based on compound (1c-2). The reaction temperature is from 0°C to the reflux temperature of the solvent and the reaction times for 2A hours.

(Step 1-17)

[0104] This step is a step wherein compound (1c-6) is obtained by oxidation of compound (1c-3). Compound (1c-6)
can be manufactured according to the methods similar to those of (Step 1-5).

[Step 1-18]

[0105] This step is a step wherein compound (1c-6) is obtained by reduction of compound (1c-4). Compound (1c-6) or can be obtained by means of the reduction reaction using a reducing agent such as disobutylaluminum hydride, sodium triethoxyaluminum hydride, and the like. There are no particular limitations on the solvent used, but in the case of a reducing reaction using a reducing agent, hydrocarbons such as toluene and ethers such as tetrahydrofuran can be used. The reducing agent is used in the amount of 1 to 2 equivalents based on compound (1c-4). The reaction temperature is from 7-8°C to come temperature, and the reaction time is from 10 millinuste to 24 hours.

[Step 1-19]

[0106] This step is a step wherein compound (1-c5) is obtained by reduction of compound (1-c4). Compound (1-c5) can be obtained either by the reduction reaction using a reducing agent such as lithium aluminum hydride or disobuty-falluminum hydride, or by catalytic hydrogenation using a Raney nickel, palledium-ceation or other catalyst in a hydrogen atmosphere. There are no perficults illinitations on the solvent used, but in the case of a reducing greation using a reducing agent, eithers such as testing-trivial control and testing-time used preferably, while in the case of catalytic hydrogenation, alcohols such as methanol, ethanol, propanol and the like can be used preferably. The reducing agent is used in the amount of 1 to 10 equivalents based on compound (1-c4). There are no particular limitations on the reaction temperature, but in the case of the reducing reaction using a reducing agent, the reaction temperature is from room temperature of the solvent used, while in the case of the catalytic hydrogenation, it has reaction temperature of the solvent used, while in the case of the catalytic hydrogenation in the reaction temperature is from room temperature to a reflux temperature of the solvent used. The reaction time is from 10 minutes to 24 hours. The atmospheric pressure in the case of catalytic hydrogenation is from 1 to 4 atms. An amount of catalyst from a catalytic imount to excess may be used in catalytic hydrogenation in the case of the catalytic from a catalytic imount to excess may be used in catalytic hydrogenation.

[Step 1-20]

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[0107] This step is a step wherein compound (1c-3) is obtained by converting the amino groups of compound (1c-5) into acetoxy groups by reacting with sodium nitrite and acetic acid, followed by hydrolysis using a base.

[0108] Acetoxylation reaction: Preferable example of the solvent used in this reaction includes a mixed solvent of acetic acid and water. More preferably, the ratio of acetic acid to water is from 1:5 to 5.1. Sodium nittle is used in the amount of 1 to 20 equivalents based on compound (1c-5). The reaction temperature is from 0°C to room temperature, and the reaction time is from 1 hour to 12 hours.

[0109] Hydrolysis reaction: There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent in this reaction include abonol solvents such as methanol and othanol, other solvents such as tetrahydrofuran; amide solvents such as N,N-dimethytformamide and N-methytpyrrolidinone; and water, dimethyt sulfoxide, mixed solvents of the foregoing and the file. Examples of the base include sodium hydrovide, potassium hydroxide, potassium carbonate and the file. The reaction temperature is from 0°C to 60°C, preferably from 20°C to 40°C, and the reaction time is from 30 minutes to 12 hours.

[0110] Compound (1c-3) can also be obtained from compound (1 c-5) by the method described as Alternative Method (1) below.

Alternative Method (1). This step is a step wherein compound (1 c-3) is obtained by healing compound (1 c-5) in the presence of a strong base. Preferable example of the solvent in this step includes diethylene glycol, and preferable example of the base includes polassium hydroxide. The potassium hydroxide is used in the amount of 51 o 30 equivalents based on compound (1 c-5), the reaction temperature is from 150°C to 230°C, and the reaction on time is from 1 hour to 12 hours. Note that during the reaction, an inactive as is nortenable ubsettitude inside the reaction container.

[Step 1-21]

[6111] This step is a step wherein compound (1 c-7) is obtained by reacting compound (1-c-6) with nitromethane in the presence of a base. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include alcohol solvents such as methanol and ethanol; ether solvents such as the tarrhydrofuran and diethyl ether, and the like. Examples of the base in this reaction include sodium methoxide, sodium ethoxide, by the like in the methodic, and it is the second include sodium methoxide, sodium ethoxide, by the like. The intrinum discorpoylamide, sodium hydroxide, potassium hydroxide, potassium carbonate, potassium theutoxide or the like. The intromethane can be used in the amount of 1 to 2 equivalents based on compound (1-c-6). The base is used in the amount of 1 to 2 equivalents bead on compound (1-c-6) and the reaction temperature is from -78°C to reflux temperature, and the reaction time is from 5 minutes to 48 box.

[Step 1-22]

- [0112] This step is a step wherein compound (1 c-8) is obtained by esterifying the hydroxyl groups of compound (1 c-7) in the presence of a base, followed by elimination in stu. There are no particular limitations on the solvent used in this reaction is along as it discoves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include either solvents such as laterihydrotran and diethyl ether; amide solvents such as IN.-Miemstyloffmamide and M-methylymrotridien, and methyleme chieride, dienthyl sulfolide, mixed solvents of the foregoing and the like. Examples of the base in this reaction include triathylamine, NIN-disporpoylethylamine and the like. Examples of the esterification agents include acetic anhydride, methanesulfonyl chioride, p-toluenesulfonyl chioride and the like. The base is used in the amount of 1.010.4.0 equivalents based on compound (1c-7). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 30 minutes to 24 hours.
- 40 [0113] Compound (1c-8) can also be obtained from compound (1c-7) by the method described below as Alternative Method (1).

Alternative Method (1): Compound (1 c-8) can be obtained by dehydrating compound (1c-7) in an acetic acid solver in the presence of an acetic acid sail. Acetic acid is used as the solvert in this reaction, but a mixed solvent in deadle acid and methanol, tetrahydrofuran and the fike can also be used. Examples of acetic acid sail include ammonium acetate, ethylene diamine diacetic acid sail and the like. The acetic acid sail is used in the amount of 1 to 20 equivalents based on compound (1c-7). The reaction temperature is from room temperature to reflux temperature, and the reaction time is form 30 minutes to 72 hours.

[Step 1-23]

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[0114] This step is a step wherein compound (10-8) is obtained by reacting compound (10-6) with nitromethane in the presence of a base, and then dehydrating by addition of an acid to the reaction system. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent used in this reaction include water, alcohol solvents such as methanol and ethanol; ether solvents such as tetrahydrofuran and diethyl ether; mixed solvents of the foregoing and the like. Examples of the base used in this reaction include sodium methoxide, sodium ethoxide, r-busyl lithium, lithium disopropylamide, sodium hydroxide, potassium bydroxide, potassium thoutoxide and the like. Examples of the acid used in this reaction include hydrochroic acid, sulfurio acid, accel acid and the like. The nitromethane is used in the amount of

1 to 20 equivalents based on compound (1c-6). The base is used in the amount of 1 to 2 equivalents based on compound (1c-6). The acid can be added in an excess amount. The reaction temperature for the reaction with infromethane is from 76°C to reflux enterperature, with a reaction in the bing from 5 minutes to 48 hours. The reaction temperature for the dehydration reaction is from room temperature to reflux temperature, with a reaction in the being from 5 minutes to 48 hours. [0115] Compound (1c-8) can also be obtained from compound (1c-6) by the method given below as Alternative Method (1).

Afternative Method (1): Compound (1c-8) can be obtained by reacting compound (1c-6) with nitromethane in the presence of an acetic acid salt. Acetic acid is used as the solvent in this reaction, but a mixed solvent of acetic acid and methanol, tetrahydrofuran and the like can also be used. Examples of the acetic acid salt used in this reaction include ammonium acetate, ethylenediamine diacetic acid salt and the like. Nitromethane is used in the amount of 1 to 10 equivalents based on compound (1c-6). The acetic acid salt is used in the amount of 1 to 20 equivalents based on compound (1c-8). The acetic acid salt is used in the amount of 1 to 20 equivalents based on compound (1c-8). The acetic acid salt is used in the amount of 1 to 20 equivalents based on compound (1c-8). The

(Step 1-24)

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[0116] This step is a step wherein compound (1c-9) is obtained by reduction of compound (1c-9). In order to obtain good results, an acid such as acetic acid or hydrochloric acid can be added. There are no particular limitations on the solvent used in this reaction as long ast dissolves the starting materials to a certain obtain without impeding the reaction. Examples of the solvents used in this reaction include alcohol solvents such as methanol and ethanol; ether solvents such as tetrahydroluran; and dimethy sultoxide and the like. Examples of the reducing agent used in this reaction include sodium borohydride, lithium borohydride and the like. The reducing agent is used in the amount of 0.5 to 3 equivalents based on compound (1c-9). The reaction temperature is form -20°C to 80°C, and the reaction time is from 10° limitudes to 12 hours. In the case of adding the acid, the acid can be added in the amount of 1 equivalent to the solvent amount based on the reducing agent.

(Step 1-25)

[0117] This step is a step wherein compound (1 c) is obtained by anionization of the nitroethyl moiety in compound (1c-9) using a base, followed by adding titanium (IV) chloride.

[0.118] Anionization reaction of compound (1-o9): There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without investing the reaction. Examples of the solvents used in this reaction include achool solvents such as methanol and ethanol; ether solvents such as sterrahydrofuran; and the like. Examples of the base used in this reaction include lithium methoxide, sodium methoxide, potassium industrials, n-buty lithium and the like. The base is used in the amount of 1 to 2 equivalents based on compound (1-o9). The 5 reaction temperature is from 7.8°C to room temperature, and the reaction time is from 5 minutes to 1 hour.

[0119] Reaction with titanium (IV) chloride: There are no particular limitations on the solvents used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include ether solvents such as tetrahydrofurar, and methylene chloride, 1,2-dichlorentenae, mixed solvents of the foregoing and the like. The titanium (IV) chloride is used in the amount of 1 to 3 equivalents based on compound (1 e-9). The reaction temperature is from -10°C to room temperature, and the reaction time is from 10 minutes to 12 hours.

(Step 1-26)

(6120] This step is a step wherein compound (1 o) is obtained by reacting compound (1 o-8) with titanium (IV) chloride in the presence of trietry/siliene. There are no particular ilmitiations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include either solvents such as tetrahydroturan; and methylene chloride, 1,2-dichlororethane, mixed solvents of the foregoing and the like. The trietry/siliane is used in the amount of 1 to 3 equivalents based on compound (1 o-8). The solution is formed to the compound the like the solution of the compound the like the solution of the solu

[Manufacturing Method 1-3-2] Method 2 for manufacturing compound (1 c)

55 [0121]

(wherein R³ is defined as above; in the formula, R¹⁵ represents a C₁₋₆ alkyl group which may be substituted with a halogen or the like; L apresents a leaving group such as a halogen atom, a p-toluenesulfonyl group and a trifluor-omethanesulfonyl group.)

[0122] Compound (1c-10), compound (1c-10-1) and compound (1 c-1 0-2) which are commercially available products can be used as is or they can also be manufactured from commercially available products by the known methods.

[Step 1-27]

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[0123] This step is a step wherein compound (1c-11) is obtained by reacting compound (1c-10) with an organophse-phorous compound, an azo reagent and compound (1c-10-1). There are no particular limitations on the solvent used in this reaction as long as It dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include either solvents such as tetrahydrofuran and diethyl ether; aromatic hydrocarbon solvents such as Ny-dimetryl(promainide and N-methylpyprolidione; ethyl acetate; acetonitrile; methylene chloride; mixed solvents of the foregoing and the like. Examples of the organo-phosphorous compound include, it include properties and the like. Examples of the organo-phosphorous compound include ester derivatives such as diethyl azodicarboxylate and disopropyl azodicarboxylate, and amide derivatives such as 1;1-(azodicarbory)(dipiperidine. Compound (1c-10-1) is used in the amount of 1 to 3 equivalents based on compound (1c-10). The azo reagent is used in the amount of 1 to 3 equivalents based on compound (1c-10). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 5 minutes to 24 hours.

[Step 1-28]

[0124]. This step is a step wherein compound (1-c11) is obtained by reacting compound (1-c10) with compound (1-c10-2), in the presence of a base. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include either solvents such as tetrahydrofurant, diethly either or the like, aromatic hydrocation solvents such as benzene, follower or the like; a manufacture of the like; a manufacture of the like; a solvent is such as methanol, ethanol or the like; dimethly sulfoxide; mixed solvents of the toregoing and the like. Examples of the base includes solvent hydroxide, sodium hydroxide, sodium entoxide, sodium entoxide, sodium entoxide, sodium carbonate, sodium carbonate and like. The base is used in the amount of 1 to 5 equivalents based on compound (1-c10-2) compound (1-c10-2) custed in the amount of 1 to 5 equivalents based on compound (1-c10). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 6 minutes to 8 hours.

[Step 1-29]

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[0125] This step is a step wherein compound (1c-12) is obtained by reacting compound (1c-11) with peroxide. Examples

of the peroxide used in this reaction include *m*-chloroperbenzoic acid, hydrogen peroxide, dimethyldioxirane, benzoyl peroxide, peracetic acid or the like. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include halogen solvents such as chloroform and methylene chloride; alcohol solvents such as methanol and ethanoi; amide solvents such as N-dimethylformamide and N-methylpyrrolidinone; aromatic hydrocarbon solvents such as benzene and toluene, diethyl ether; acetione; acetionitrile; acetic acid, water or the like. Peroxide is used in the amount of 1 to 5 equivalents based on compound (1c-11). The reaction temperature is from -40°C to reflux temperature, and the reaction time is from 1 minute to 48 hours.

10 [Step 1-30]

[0128] This step is a step wherein compound (1c-13) is obtained by reacting compound (1c-12) with an acid anhydride used in this reaction include acetic anhydride, trifluoroacetic acid anhydride, or the like. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the sovent include halogen solvents such as chirorform and methylene chloride; aromatic hydrocarbon solvents such as benzene and foluene; accide acid, frilluoroacetic acid or the like. Acid anhydride can also be used as the solvent. Acid anhydride is used in the amount of 1 equivalent to excess based on compound (1c-12). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature.

(Step 1-31)

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[0127] This step is a step wherein compound (10-14) is obtained by hydrolyzing compound (10-13), Compound (10-14) can be obtained by hydrolyzing compound (10-13), for instance, in the presence of an acid such as sulfuric acid, or, for instance, in the presence of an acid such as sulfuric acid, or, for instance, in the presence of an acid such as sulfuric acid, or, for instance, in the presence of an akidal such as sodium hydroxide, potassium hydroxide, sodium methoxide, potassium carbonate or sodium carbonate. There are no particular limitations on the solvent used in this reaction sellong as it alsolves the starting materials to a certain extent whitout impeding the neaction. Examples of the solvent include either solvents such as as 1.4-dioxane and tetrahydroduran; alcohol solvents such as methanol and ethanol; halogen solvents such as methylene chioride and chioroform; aromatic hydrocarbon solvents such as benzane and toluren; amide solvents such as NA-dimethylformamide and N-methylpyrrolidinone; dimethyl sulfoxide, acetonitrile, water, mixed solvents of the foregoing or the like. The acid or the base is used in the amount of 1 equivalent to excess based on compound (10-13). The reaction times if form 0°C to reflux temperature, and the reaction time is form 0°C to reflux temperature, and the reaction time is form 0°C to reflux temperature.

[Step 1-32]

[0128] This step is a step wherein compound (1c-15) is obtained by converting the hydroxyl group of compound (1c-14) to a leaving group.

[0128] When Li is a methanesulfonyloxy group, p-toluenesulfonyloxy group or other sulfurio acid ester; compound (1-61) can be obtained by reacting compound (1-614) with sulfonyl chloride under basic conditions. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as 1-4-dioxane and tolerary increase and tolerary mide solvents such as NIA-dimethylformamide and N-methylyprolidinone; and dimethyl sulfoxide, methylene chloride, mixed solvents of the foregoing and the like. Examples of the base include triethylamine, NIA-diisopropylethylamine and the like. Examples of the sulfonyl chloride include methanesulfonyl chloride and the like. The base is used in the amount of 1 to 3 equivalents based on compound (1c-14). The sulfonyl chloride is used in the amount of 1 to 2 equivalents based on compound (1c-14). The sulfonyl chloride is used in the amount of 1 to 2 equivalents based on compound (1c-14). The prediction temperature is from CCI to norm temperature, and the reaction time is from 10 minutes to 24 hours.

[0130] When L is a chlorine atom or a bromine atom; compound (1o-15) can be obtained by halogeneting compound (1o-14) with terchiorhoremchane or tetrabromomethane or tetrabromomethane or triphorephosphine. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a cartain extent without impeding the reaction. Exemples of the solvent include either solvents such as tetrahydrofurari, emide solvents such as N,N-dimetryliformamide and N-methylyprolidinone; and methylene chloride, mixed solvents of the foregoing and the like. The tetrachioromethane or tetrabromomethane can also be used as the solvent. The triphenylphosphine is used in the amount of 1 to 2 equivalents based on compound (1c-14). The trizenbromomethane is used in the amount of 1 equivalent to the solvent amount based on compound (1c-14). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10°C influx temperature, and the reaction time is from 10°C influx temperature, and the reaction time is from 10°C influx temperature.

[0131] Compound (1c-15) can also be obtained from compound (1c-14) according to the methods described below as Alternative Methods (1), (2) and (3). Alternative Method (1): Compound (1c-14) can be converted into compound (1c-

15) under acidic conditions. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include ether solvents such as diethyl ether, water, ethyl acetate, mixed solvents of the foregoing and the like. In this reaction, a phase-transfer agent such as tetrabutylammonium bromide can be used in the amount of 0.01 to 2 equivalents based on compound (1c-14). Examples of the acid include hydrochloric acid, hydrobromic acid and the like. Sulfuric acid can also be added to obtain good results. The reaction temperature is from 0°C to room temperature, and the reaction time is from 10 minutes to 12 hours. Alternative Method (2): Compound (1c-15) can be obtained by reacting compound (1c-14) with thionyl chloride. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include aromatic hydrocarbon solvents such as benzene and toluene; and acetonitrile, chloroform, methylene chloride and the like, and the thionyl chloride can also be used as the solvent. Pyridine can also be added to the reaction in a catalytic amount to improve the yield. The thionyl chloride is used in the amount of 1 equivalent to the solvent amount based on compound (1c-14). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 12 hours. Alternative Method (3): Compound (1c-15) can be obtained by reacting compound (1c-14) with phosphorus halide. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include ether solvents such as diethyl ether; N,N-dimethylformamide, acetonitrile, chloroform and the like. Examples of the phosphorus halide include phosphorus oxychloride, phosphorus trichloride, phosphorus tribromide and the like. The phosphorus halide is used in the amount of 0.33 to 3 equivalents based on compound (1 c-14). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 12 hours.

[Step 1-33]

[0132] This step is a step wherein compound (1c-16) is obtained by converting the leaving group of compound (1c-16) to a cyano group. To obtain good results, an incognic salt such as sodium iodition or the like may also be added in the emount of 1 to 2 equivalents based on compound (1c-15). Examples of the cyanization agent used in this reaction include sodium cyanide, batestum cyanide, inthin waynide or the like. There are no particular inhitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include alcohol solvents such as methanol and ethanol; either solvents such as 1,4-dioxane and terranydrofuran; amides solvents either foregoing or the like. The cyanisation agent is used in the amount of 1 to 5 equivalents based on compound (1c-15). The reaction temperature is from nom temperature to reflux temperature, and the reaction limits from 50 mixtures to 45 mixtures.

5 [Step 1-34]

[0133] This step is a step wherein compound (1c-17) is obtained by reacting compound (1c-16) with hydroxy ammonium choride. Examples of the base used in this reaction include pyridine, sodium acetate, potassium acetate, sodium bicarbonate, sodium carbonate, sodium hydroxide, potassium hydroxide or the like. There are no particular limitations on the sovent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include hadopenated hydroxarbons such as a fide/horomethalene and chloroforms; toloxides such as dimethyl sulfoxide; etners such as leterally reforum and 1,4-dioxane; alcohols such as methanol and ethanol; amides such as N-methylpyrrolidinone, N,N-dimethylformamide and N,N-dimethylforete such as nethanol and ethanol; amides such as N-methylpyrrolidinone, N,N-dimethylformamide and N,N-dimethylforete profile; water, mixed solvents of the foregoing, or the like. Hydroxylermonium chloride is used in the amount of 1 to 5 equivalents based on compound (1c-16). The base is used in the amount of 1 to 4 equivalent because based on compound (1c-16). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time is from 10°C to reflux temperature, and the reaction time i

[Step 1-35]

50 [0134] This step is a step wherein compound (1c-18) is obtained by reacting compound (1c-17) with sodium hirite and a chlorine source. Examples of the chlorine source used in this reaction include hydrochloric acid, copper chloride or the like. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include ether solvents such as 1.4-dioxane and terrahydrofunan; amide solvents such as N.N-dimethyllomamide and N-methylpymodificnors, dimethyl sulfocks, according a certain production and a continuous c

[Manufacturing Method 1-3-3] Method 1 for manufacturing compound (1c-1):

[0135]

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HO-R²
(1c-19)
HO-R²
(1c-19)
HO-R²
(1c-19-1)
HO-R²
(1c-19-1)
HO-R²
(1c-19-1)
[1c-20-1)
[1c-20-1]

(wherein R3 and L are defined as above.)

[0136] Compound (1c-19), compound (1c-20), compound (1c-19-1) and compound (1c-20-1) which are commercially available products can be used as is, or they can be obtained from commercially available products by the well known methods.

[Step 1-36]

[0137] This step is a step wherein compound (1c-21) is obtained by reacting compound (1c-19) with compound (1c-19-1) in the presence of a base. Compound (1 c-21) can be manufactured according to the methods similar to those of (Step 1-28).

30 [Step 1-37]

[0138] This step is a step wherein compound (1c-21) is obtained by reading compound (1c-20) with an organophosphorous compound, an azo reagent and compound (1c-19-1). Compound (1c-21) can be manufactured according to the methods similar to those of [Step 1-27].

[Step 1-38]

[0138] This step is a step wherein compound (10-21) is obtained by reacting compound (10-20) with compound (10-20) in the presence of a base. A catalytic amount of sofurin oidie, potassium iodies or tertabulysimmonium losidies can be added to obtain good results, and a copper catalyst can also be added in order to obtain good results. There are no particular limitations on the solvent used in this reaction had in this reaction to hotel may be active when the section with the soft without impeding the reaction. Examples of the solvents used in this reaction include either solvents such as tetrahydrofuran and diethyl either, aromatic hydrocarbon solvents such as benzene and toluene; smide solvents such as N.A-directly/marmidie and N.A-methylyprodificiones; acloud is solvents such as methanol and ethanol; and dimethyl sulfoxide, mixed solvents of the foregoing and the like. Examples of the base include sodium hydride, potassium robunde, sodium methodie, N.N.-diisopropylethylamine, triethylamine, potassium hydroxide, sodium methodie, sodium methodie, sodium hydroxide, sodium sodium enaborate and the like. Examples of the copper catalysts include copper, opper (I) loolide, copper (I) broinide, copper (I) sued in the amount of 1 to 5 equivalents based on compound (10-20). The seas is used in the amount of 1 to 5 equivalents based on compound (10-20). The reaction femerature is from 5 mitutes to 48 hours.

[Manufacturing Method 1-3-4] Method 2 for manufacturing compound (1c-1):

5 [0140]

(wherein R3 is defined as above.)

[0141] Compound (1c-22) and Compound (1c-10-1) may be commercially available products or can also be manufactured from the commercially available products by the well known methods.

(Step 1-39)

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[0142] This step is a step wherein compound (1c-23) is obtained by reacting compound (1c-22) with compound (1c-01-1) in the presence of a base. A copper catalyst can also be added in this reaction. There are no particular initiations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include either solvents such as tetrahydrofuran and diethyl ether; aromatic hydrocarbon solvents such as betrazene and tollouens; anide solvents such as the Nuclimetry information and N-methylpyrrolldinone; alcohol solvents such as methanol and ethanol; and dimethyl sulfoxide, mixed solvents of the freeging and the like. Examples do the base include sodium hydrock, postium thotwork, sodium methoxide, potassium butwork, sodium methoxide, opoper (i) bromide, copper (i) chirofice and the like. Examples of the copper catalyst include copper, copper (i) lodde, opoper (i) bromide, copper (i) chirofice and the like. Examples of the copper catalyst include copper, copper on compound (1c-10-1). Compound (1c-10-1) is used in the amount of 1.0 to 3.0 equivalents based on compound (1c-10-1). The reaction the incompound (1c-10-1). The reaction the incompound (1c-10-1). The reaction of the principle of the copper catalyst can be used in the amount of 0.01 to 1 equivalents based on compound (1c-10-1). The reaction the incompound (1c-10-1). The reaction of the principle of the copper catalyst can be used in the amount of 0.01 to 1 equivalents based on compound (1c-10-1). The reaction of the copper catalyst can be used in the amount of 0.01 to 1 equivalents based on compound (1c-10-1). The reaction of the copper catalyst can be used in the amount of 0.01 to 1 equivalents based on compound (1c-10-1). The reaction of the copper catalyst can be used in the amount of 0.01 to 1 equivalents based on compound (1c-10-1). The reaction of the copper catalyst can be used in the amount of 0.01 to 1 equivalents based on compound (1c

[Manufacturing Method 1-3-5] Method 3 for manufacturing compound (1c-1), (1c-2) and (1c-6)

[0143]

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(wherein Hal, L, \mathbb{R}^3 , \mathbb{R}^{19} is defined as above; in addition, \mathbb{R}^{16} and \mathbb{R}^{17} represent a halogen group, a $\mathbb{C}_{1,6}$ alkyl group and a $\mathbb{C}_{1,6}$ alkoy group; Hal¹ represents a chlorine atom and a bromine atom; \mathbb{M}^1 represents a magnesium atom and a \mathbb{Z} inc atom.)

[0144] Compound (1c-24), compound (1c-25), compound (1c-19-1), compound (1c-20-1), compound (1c-24-1) and compound (1c-26-1) which are commercially available products can be used as is, or they can be manufactured from commercially available products by the known methods.

Step 1-401

[0145] This is a step wherein compound (1c-25) is obtained by converting compound (1c-24) into an organometallic compound by substituting a metal atlom for a haloger atlom of compound (1c-24), and then applying a formylaffler greagent. There are no particular limitations on the solvent used in this step as long as it dissolves the starting materials to a certain organization of the starting materials to a certain organization of the starting materials to a certain organization organization compounds distained by applying a base such as 7-bully lithium, 2-bully lithium, 7-bully lithium or the like. The temperature at which the organolithium compound is to be prepared is from -100°C to room temperature, and preferably from -78°C to 40°C. The base can be used in the amount of 1 to 12 equivalents based on compound (1c-24), and the reaction time is from 10 minutes to 24 hours. Examples of the formylating reagent include N,N-dimethyl-15 formamide, N-formylphorpholine, N-methylformanilide or the like. The formylating reagent can be used in the amount of 1 to 26 equivalents based on compound (1c-24), and preferably to 2 equivalents. The temperature for reacting the organometallic compound and the formylating reagent is from -78°C to room temperature, and the reaction time is from 5 minutes to 24 hours.

20 [Step 1-41]

[0.145] This step is a step wherein compound (10-25) is obtained by protecting the formity group of compound (10-25) with an acetal, in the presence of an alcohol and an acid catalyst. Preferable exmaples of alcohol used in this reaction include methanol, ethylane glycol, procylene glycol or the like. Examples of the acid catalyst include hydrochloric acid, softwice acid, protolere sufficient acid, activate acid, protolere sufficient acid, acetic acid, ammonium chloride or the like. There are no particular limitations on the solvent used in this step as long as it dissolves the starting metaletis to a certain scent without impeding the reaction. Examples of the solvent include alcohol solvents such as methanol, ethanol and ethylene glycol; aromatic hydrocarbon solvents such as benzene and toluene; halogenated hydrocarbon solvents such as dictional such as dischol is used in the amount of 1 equivalent to the solvent amount based on compound (10-25). The acid catalysts is used in the amount of 0.05 equivalents to excess based on compound (10-25). The reaction interesting in form come imperiative is from come imperiative.

[Step 1-42]

38 [0147] This step is a step wherein compound (1c-27) is obtained by converting compound (1c-28) into an organometallic compound by substituting a metal atom for a halogen atom of compound (1c-28), and then applying a formylation reagent. Compound (1c-27) can be manufactured according to the methods similar to those of [Step 1-15].

[Step 1-43]

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[0148] This step is a step wherein compound (10-28) is obtained by reducing compound (10-27). Examples of the reducing agent used in this reaction include sodium borohydride, lithium borohydride, lithium burnhumhydride, or the file. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include alcohol solvents such as methand and ehanoit either solvents used as deithyl either and tetrahydrofuran; carnetic hydrocarbon solvents such as methand toluene; halogenated hydrocarbon solvents such that exhibit solvents are desirable when using a reducing eigent such as sodium borohydride; their solvents are desirable when using a reducing eigent such as sodium borohydride; their solvents are desirable when using a reducing agent such as lithium aluminumhydride. The reducing agent is used in the amount of 0.25 to 4 equivalents based on compound (10-27). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 6 miluste to 24 hours.

[Step 1-44]

[0149] This step is a step wherein compound (1o-29) is obtained by reacting compound (1o-28) and compound (1o-20-1), in the presence of a base. Compound (1o-29) can be obtained according to the methods similar to those of [Step 1-38].

[Step 1-45]

[0150] This step is a step wherein compound (1c-30) is obtained by reacting compound (1c-24) and compound (1c-24-1), in the presence of a base. Compound (1c-30) can be manufactured according to the methods similar to those of (Step 1-39).

(Step 1-46)

[0151] This step is a step wherein compound (1c-31) is obtained by reading compound (1 c-24) and compound (1c-19-1), in the presence of a base. Compound (1c-31) can be manufactured according to the methods similar to those of (Step 1-38).

(Step 1-47)

156 [0152] This step is a step wherein compound (1c-32) is obtained by converting compound (1c-31) into an organomatallic compound by substituting a metal atom for a halogen atom of compound (1 c-31), and then reacting with a formylating agent. Compound (1c-32) can be manufactured according to the methods similar to those of (Step 1-15).

[Step 1-48]

[0153] This step is a step wherein compound (1 c-32) is obtained by reacting compound (1c-25) and compound (1c-19-1), in the presence of a base. Compound (1c-32) can be manufactured according to the methods similar to those of (Step 1-39).

25 [Step 1-49]

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[0155] In addition, when M is a zinc atom, compound (1-26-1) can be prepared in situ and used in the reaction, as describe below. The reaction in [Step 1-49] can be carried out by synthesizing compound (1-26-1) in situ using benzyl halide and advivated zinc. In this case, the activated zinc is used in the amount of 1 to 1.3 equivalents based on benzyl halide. The reaction temperature for obtaining compound (1-26-1) is from -10°C to room temperature, preferably from -5°C to 10°C, and the reaction time is from 1 hour to 10 hours.

[Manufacturing Method 1-3-6] Method 1 for manufacturing compound (1c-2)

[0156]

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(wherein R18, R19, R20 and R21 represent a halogen, a C1-6 alkyl group and a C1-6 alkoxy group.)

[0157] Compound (1c-34), compound (1c-34-1), compound (1c-34-2), compound (1c-34-3) and compound (1c-34-4) which are commercially available products can be used as is, or they can also be manufactured from commercially available products by the known methods.

(Step 1-50)

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[0158] This step is a step wherein compound (1c-3d) is obtained by converting compound (1c-3d) into an organometatic compound by substituting a metal atom for a halogen atom of compound (1c-3d), and then reacting with compound (1c-3d-1). There are no particular initiations on the solvent used in this reaction as long as it dissolves the starting materials to a certain action without impeding the reaction. Preferable examples of the solvent include other solvents such as tetrahydrofuran and diethyl ether. Examples of the organometallic compound include organofitiation compounds obtained by applying a base such as n-butyl lithium, shutyl lithium, shutyl lithium, flistinum discopropyl amide, or the like. The temperature at which the organotishium compounds to be prepared is form 78°C to room temperature, preferably from -78°C to -40°C. The base is used in the amount of 1 to 1.5 equivalents based on compound (1c-3d-1). The reaction time is from 30° mitures to 2d hours. Compound (1c-3d-1) is used in the amount of 1 to 2 equivalents based on compound (1c-3d-1) is from -78°C to room temperature, preferably from representating the properature for reacting the organometallic compound and compound (1c-3d-1) is from -78°C to room temperature, preferably from is from 50° miture to 10° page 10° page

9 [Step 1-51]

[0159] This step is a step wherein compound (1o-35) is obtained by reacting compound (1o-34) and compound (1o-34-2), in the presence of a base. There are no particular imitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include other solvents such as tetrahydrofuran and diethyl ether, aromatic hydrocarbon solvents such as benzene and toluene; amide solvents such as N-1-dimethyltremmids and N-methyltremidisence, school solvents such as methanol and ethanoit dimethyl sulfoxide, mixed solvents of the forgoing, or the like. Examples of the base include sodium hydride, potassium blurboxide, sodium ethoxide, sodium methoxide, sodium methoxide, sodium ethoxide, sodium methoxide, consument of 1 to 2 equivalents based on compound (1o-34). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 5 minutes to 24 hours.

(Step 1-52)

[6] [160] This step is a step wherein compound (1 c-36) is obtained by converting compound (1c-34) into an organometallic compound by substituting a metal atom for a halogen atom of compound (1c-34), and then reacting compound (1c-34-3). Compound (1c-36) can be manufactured according to the methods similar to those of [Step 1-50].

[Step 1-53]

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[0161] This step is a step wherein compound (1c-36) is obtained by reacting compound (1c-34) and compound (1c-34-4) in the presence of a base. Compound (1c-36) can be manufactured according to the methods similar to those of (5tep 1-51).

Manufacturing Method 1-3-7] Method 2 for manufacturing compound (1c-2)

[0162]

(wherein Hal is defined as above; R22 and R23 represent a halogen atom, a C1.6 alkyl group and a C1.6 alkoxy group.)

[0163] Compound (1 c-37) and compound (1 c-37-1) which are commercially available products can be used as is, or they can be manufactured from commercially available products by the known methods.

(Step 1-54)

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[0164] This step is a step wherein compound (1c-38) is obtained by converting compound (1c-37) into an organometalitic compound by substituting a metal atom for the hydrogen atom at position 5 of compound (1c-37), and then reacting with compound (1c-37-1). There are no particular inhibitors on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Preferrable examples of the solvent include either solvents such as letrahydrofluran and diethyl either. Examples of the organometallic compound include organolithium compounds obtained by applying a base such as n-butyl tithium, s-butyl tithium, ibitum discopropyl arnicle or the like. The temperature withinh the organolithium compound is 10 be preparted is from 2°C to room temperature, preferably from -78°C to room temperature, preferably from -78°C to room temperature. The reaction time is from 50 minutes to 24 hours. Compound (1c-37) is used in the amount of 1 to 2 equivalents based on compound (1c-37). The temperature for reacting the organometallic compound and compound (1c-37-1) is from -78°C to room temperature. The reaction time is from 50 minutes to 21 hours.

[Manufacturing Method 1-3-8] Method 1 for manufacturing compound (1c-3):

20 [0165]

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30 (wherein R³ and L are defined as above.)

[0166] Compound (1c-39) and Compound (1c-20-1) may be commercially available products or can also be manufactured from the commercially available products by the well known methods.

[Step 1-55]

[0167] This step is a step wherein compound (1c-40) is obtained by reacting compound (1c-39) with compound (1c-20-1). Compound (1c-20-1) is used in the amount of 0.2 to 1.0 equivalents based on compound (1c-39). Compound (1c-40) can be manufactured according to the methods similar to those of (Step 1-38).

40 [Manufacturing Method 1-3-9] Method 2 for manufacturing compound (1c-3):

[0168]

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(wherein R3, R13, R13 and Hal are defined as above.)

[0169] Compound (1c-41) and compound (1c-41-1) may be commercially available products or can also be manufactured from the commercially available products by the well known methods.

[Step 1-56]

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[0170] This step is a step wherein the halogen atom in compound (16-41) is replaced with a metal atom to obtain an organometalic compound (in-45). There are no particular limitations on the solvent used in this reaction as long as it discoives the starting metarfals to a certain extent without impeading the nearcion. Exemples of the solvents used in this reaction include either solvents can be a steraivy/or-furan and diethyl ether; aromatic hydrocarbon solvents used in the reaction include either solvents could be recorded in the solvents of the foregoing and the like. Examples of the reagent for converting compound (16-41) into an organometalic compound include *nburyl initium, *e.buryl initium, *e.buryl inagnesium-bromide, entry inagnesium-diofied, magnesium-solvent, magnesium, zinc and the like. The reagent for converting compound (16-41) into an organometalic compound is used in the amount of 16-3 equivalents based on compound (16-41). The reaction temperature in the reaction for converting compound (16-41) into an organometatic compound (16-41). The reaction temperature in the reaction for converting compound (16-41) into an organometatic compound (16-41). The reaction temperature in the reaction for converting compound (16-41) into an organometatic compound (16-41). The reaction temperature in the reaction the being from 10 minutes to 12 hours. The reaction temperature in the reaction of adding compound (16-41) is from .78°C to room temperature, with a reaction time being from 10 minutes to 18 hours. The reaction time being from 10 minutes to 18 hours.

[Step 1-57]

40 [0171] This step is a step wherein compound (1 c-43) is obtained by deprotecting the acetal of compound (1c-42). Compound (1c-43) is manufactured according to the methods similar to those of [Step 1-16].

[Step 1-58]

[0172] This step is a step wherein compound (1 c-43) is obtained by reacting compound (1-c-41) with compound (1-d-1-), in this step, compound (1-d-2) is obtained according to the methods similar to those of [Step 1-56], after which are acid is added in the reaction system or at the work-up stage to obtain compound (1-d-3). Examples of the acids used in this reaction include inorganic acids such as hydrochloric acid, sulfuric acid and hydrobromic acid; calcid side gives and the file. The acid can be used in the amounts of from the catalytic amount to the solvent amount based on Compound (1c-41). The reaction temperature is from O'Ct to the reflux temperature of the solvent, and the reaction time is from 5 minutes to 24 hours.

[Step 1-59]

[0173] This step is a step wherein compound (1-44) is obtained by reducing compound (1-43). There are no particular imitiations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvents used in this reaction include either solvents such as tetrahydrofuran and diethly either aromatic hydrocarbon solvents such as bezerves and toluene; and the like. Examples of the reduction.

agent include lithium aluminum hydride-aluminum chloride and the like. The lithium aluminum hydride is used in the amount of 2 to 6 equivalents based on compound (1c-49). The aluminum chloride is used in the amount of 2 to 9 equivalents based on compound (1 c-43). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 48 hours.

[Manufacturing Method 1-3-10] Method 3 for manufacturing compound (1c-3)

[0174]

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(wherein Hal is defined as above; R²⁴ represents a hydrogen atom, a halogen, a C₁₋₆ alkyl group and a C₁₋₆ alkoxy group, or the like.)

[0175] Compound (1c-45) and compound (1c-45-1) which are commercially available products can be used as is or they can also be manufactured from commercially available products by the known methods.

[Step 1-60]

[0176] This step is a step wherein compound (1c-46) is obtained by reacting compound (1c-45) and compound (1c-45). If or instance, in a solvent such as terralyordorum, Nu-dimethyloromaide or dimethyls publickle, for instance, in the presence of a base such as potassium rbutoxide. Compound (1c-45-1) is used in the amount of 1 to 1.5 equivalents based on compound (1c-45). The reaction in the instance is used in the amount of 1 to 1.5 equivalents based on compound (1c-45). The reaction the reaction thin is from 30 minutes to 24 hours.

[Step 1-61]

[0177] This step is a step wherein compound (1c-47) is obtained by reducing the compound (1c-46). Compound (1c-47) can be manufactured according to the methods similar to those of [Step 1-4].

[Manufacturing Method 1-3-11] Method 4 for manufacturing compound (1c-3)

40 [0178]

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(wherein R⁹, R⁷ and Hal are defined as above; in addition, R²⁶ represents a C_{1,6} alkyl group.) [0179] Compound (1c-48) and compound (1c-41-1) which are commercially available products can be used as is, or they can be manufactured from commercially products by the known methods. [Step 1-62]

[0180] This step is a step wherein compound (16-49) is obtained by substituting a phosphorus atom for a halogen atom of compound (16-48). This reaction is carried out by mixing compound (16-48) and trially/phosphite in a solvent or in the absence of solvent, and heating. There are no particular limitations on the solvent used in this reaction as long as it dissolves the staffing materials to a certain extent without impeding the reaction. Examples of the solvent include aromatic hydrocarbon solvents such as toluene and xylene or mixed solvents of the foreigning. The trially/phosphite is added in the amount of 1 to 1.2 equivalents based on compound (16-48). The reaction temperature is from 100°C to 150 °C, and the reaction time is from 30 minutes to 2 hours.

(Step 1-63)

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[0181] This stop is a step wherein compound (16-50) is obtained by adding a base to compound (16-49) and then reacting with compound (16-41-1). There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as tetrahydrofuran and 1,4-dioxane; amide solvents such as /N/Adimethyflormamide and /N-methytipyroidinone; or mixed solvents of the foregoing. Examples of the base include metal hydrides such as sodium hydride and potassium hydride; metal alcoholates such as sodium methoxide and potassium in butoxide. Compound (16-41-1) is added in the amounts of 1 to 2 equivalents based on compound (16-49). The reaction temperature is from room temperature to 80°C, and the reaction time is from 30 minutes to 12 hours.

(Step 1-64)

[0182] This step is a step wherein a double bond of compound (1c-50) is hydrogenated, leading to compound (1c-51). This step is a reaction whereby hydrogen addition is carried with compound (1c-50) he solvent, under a hydrogen atmosphere, and using a metal catalyst. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include ether solvents such as tetrahydrofurar and (1,4-dioxane; alcohol solvents such as methanol and ethanol; ester solvents such as ethyl acetate or mixed solvents of the foregoing. Examples of the metal catalyst include palladium (1) oxide, plantium (10) oxide, and the metal catalyst is used in a catalytic amount to excess based on compound (1c-50). The reaction temperature is from room temperature to 80°C, the reaction time is from 5 minutes to 24 hours. The reaction pressure is from 1 atmosphere to 4 atmosphere to 4

[Step 1-65]

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[0183] This step is a step wherein alcohol product (1c-52) is obtained by reducing the ester group of compound (1c-51). There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as either and tetrahydrofurar; aromatic hydrocarbon solvents such as toluene and xylen; or mixed solvents of the foregoing. Examples of the reducing agent include soldim borohydride, filthium aluminum hydride, dislocutylaluminum hydride, or the like. The reducing agent is added in the amount of 0.5 to 2 equivalents of compound (1 c-51). The reaction temperature is from -20°C to reflux temperature of the solvent, and the reaction time is from 10 minutes to 24 hours.

[Manufacturing Method 1-3-12] Method 5 for manufacturing compound (1c-3)-

[0184]

(wherein R26 and R27 represent a halogen atom, a C1.6 alkyl group and a C1.6 alkoxy group.)

[0185] Compound (1c-53) and compound (1c-53-1) which are commercially available products can be used as is, or they may be manufactured from commercially available products by the known methods.

[Step 1-66]

[0186] This step is a step wherein compound (1c-54) is obtained by reacting compound (1c-53) and compound (1c-53-1). There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include alcohol solvents such as ethanol and methanol, or the like. Compound (1c-53-1) is used in the amount of 1 to 2 equivalents based on compound (1c-53). The reaction temporature is the reful temporature. and the reaction itemporature is the reful temporature.

[Step 1-67]

15 [0187] This step is a step wherein compound (1c-55) is obtained by reducing compound (1c-54). Compound (1c-55) can be manufactured according to the methods similar to those of [Step 1-4].

[Manufacturing Method 1-3-13] Method 1 for manufacturing compound (1c-4):

20 [0188]

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(wherein R3 and Hal are defined as above.)

[0189] Compound (1c-56), compound (1c-58), compound (1c-60), compound (1c-62), compound (1c-64), compound (1c-64), compound (1c-64), compound (1c-64), compound (1c-64), compound (1c-66), which are commercially available products can be used as is, or they can also be manufactured from the commercially available products by the well known methods.

Istep1-731

(1c-64)

[Step 1-68]

[0190] This step is a step wherein compound (1c-57) is obtained by reacting compound (1c-58) with compound (1c-59-1) in the presence of a base. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent used in this reaction include either solvents such as tetrahydrofurum; amide solvents such as N,N-dimethyllomamide and N-methyrytoridinone actional solvents such as methand and ethand; and dimethy silloridis, mixed solvents of the foregoing and the like. Examples of the base include sodium hydride, potassium Putrovide, sodium ethoxide, sodium ethoxide, sodium methoxide, N,N-dilappropylethylamine, triethylamine, potassium hydroxide, sodium hydroxide, potassium carbonate, sodium robonate and the like. The base is used in the amount of 1 to 5 equivalents based on compound (1c-19-1). Compound (1c-19-1) is used in the amount of 1 equivalent to the solvent amount based on compound (1c-59.) The reaction temperature is from come temperature for efflux temperature is from come temperature for efflux temperature, and the reaction time is from 30 minutes to 48 hydroxides.

(Step 1-69)

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[0191] This step is a step wherein compound (1c-59) is obtained by reacting compound (1c-58) with compound (1c-19-1). Compound (1c-59) can be manufactured according to the methods similar to those of [Step 1-37].

[Step 1-70]

[0192] This step is a step wherein compound (1c-59) is obtained by reacting compound (1 c-60) with compound (1 c-19-1). Compound (1 c-59) can be obtained according to the methods similar to those of [Step 1-36].

[Step 1-71]

[0193] This step is a step wherein compound (1c-61) is obtained by reacting compound (1c-56) with compound (1c-56-1) in the presence of a palladium catalyst. A phosphine ligand can also be added to the reaction system to obtain good results. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent in this reaction include ether solvents such as 1,4-dioxane and tetrahydrofuran; alcohol solvents such as methanol and ethanol; aromatic hydrocarbons solvent such as toluene and xylene; amide solvents such as N,N-dimethylformamide and N-methylpyrrolidinone; and dimethyl sulfoxide, mixed solvents of the foregoing and the like. Examples of palladium catalyst include palladium (II) acetate, tris(dibenzylidenacetone)dipalladium (0), dichlorobis(triphenylphosphine)palladium (II), dichlorobis(tri-o-tolylphosphine) palladium (II), bis(tri-t-butylphosphine)palladium (0), tetrakis(triphenylphosphine)palladium (0), palladium (0) pentadienone and the like. Examples of the phosphine ligand include triphenylphosphine, tri-o-tolylphosphine, tri-f-butylphosphine, diphenylphosphinoferrocene, 2-dicyclohexylphosphinobiphenyl, 2-di-t-butylphosphinobiphenyl, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) and the like. Examples of the base include sodium t-butoxide, cesium carbonate, potassium carbonate, potassium phosphate and the like. Compound (1c-56-1) is used in the amount of 1 equivalent to excess based on compound (1c-56). The palladium catalyst is used in the amount of 0.01 to 0.3 equivalents based on compound (1c-56). The phosphine ligand is used in the amount of 0.01 to 1.2 equivalents based on compound (1c-56). The base is used in the amount of 1 to 4 equivalents based on compound (1c-56). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 30 minutes to 72 hours.

[Step 1-72]

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[0194] This step is a stop wherein compound (1c-66) is obtained by a reductive amination in which compound (1c-67) is reacted with compound (1c-56-1). Acedic acid can also be added to promote the reaction. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent in this reaction include other solvents such as 1,4-dioxane and tetrahydruran; alcohol solvents such as methanol and entherine chiloride, mixed solvents of the requiring and the like. Examples of the reducing agent include lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, sodium bracedoxyborohydride, 2-picoline-borane and the like. Compound (1c-66-1) is used in the amount of 1 to 2 equivalents based on compound (1c-62). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 1.0 minuses by 42 hours.

[Step 1-73]

[0196] This step is a step wherein compound (1c-65) is obtained by a reductive amination in which compound (1c-64) is reacted with compound (1c-41-1). Compound (1c-65) can be manufactured according to the methods similar to those of (Step 1-72).

[Manufacturing Method 1-3-14] Method 2 for manufacturing compound (1c-4):

[0196]

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(wherein R3 and Hal are defined as above.)

[0197] Compound (1c-56) and compound (1c-41-1) which are commercially available products can be used as is, or compound (1c-56) and compound (1c-41-1) can also be manufactured from commercially available products by the well known methods.

(Step 1-74)

[0198] This step is a step wherein compound (1 c-66) is obtained by reacting compound (1c-56) with compound (1c-41-1). Compound (1c-66) can be manufactured according to the methods similar to those of [Step 1-56].

[Step 1-75]

[0199] This step is a step wherein compound (1o-67) is obtained by reducing compound (1o-68) with indotrimethylsilane. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Exemples of the solvent include either solvents such as tetra/producinar, and acctonitrile, methylene chloride and the like, preferably methylene chloride and sectonitrile. The lodotrimethylsilane is used in the amount of 2 to 10 equivalents based on compound (1o-66), the reaction temperature is from 0°C to 60°C, and the reaction time is from 5 minutes to 8 hours. The indotrimethylsilane used in the reaction may be a commercially available product, or may be prepared at the time of use by reacting sodium iodide and chlorotrimethylsilane in acetonitrile at room temperature.

[Manufacturing Method 1-3-15] Method 3 for manufacturing compound (1c-4):

[0200]

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(wherein R³ is defined as above, and Q represents a sulfur atom and oxygen atom.)

[0201] Compound (1c-68) and compound (1c-41-1) which are commercially available products can be used as is, or they can also be manufactured from the commercially available products by the well known methods.

[Step 1-76]

[0202] This step is a step wherein one of the bromide atoms in compound (1 c-68) is aninoinzed using an organometallic reagent, which is reacted with compound (1c-41-1), then the other bromide atom in compound (1c-68) is anionized by adding the further organometallic reagent in the same container, which is then reacted with a cyanization reagent to obbin compound (1 c-89). There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as tetrahydroturan and diethyl ether; aromatic hydrocarbon solvents such as benzene and toluene; mixed solvents of the foregoing and the like. Examples of the organization reagent include z-buyl filtium, aboutly filtium and the like. Perferable examples of the oparization reagent include z-butheresulforly cyanide. The organizational reagent is used in the total amount of 2 to 3 equivalents based on compound (1c-68). Compound (1c-41-1) is used in the amount of 1 to 1.5 equivalents based on compound (1c-68). The reaction temperature is from -78°C to room temperature, and the reaction time is from 10 minutes to 24 hours.

(Step 1-77)

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[0203] This step is a step wherein compound (1 c-70) is obtained by reducing compound (1c-69). Compound (1c-70) can be manufactured according to the methods similar to those of [Step 1-75].

[Manufacturing Method 1-3-16] Method 1 for manufacturing compound (1c-5):

[0204]

(wherein R3 is defined as above.)

[0205] Compound (1 c-66) can be manufactured from a commercially available product by the well known methods, or compound (1c-66) can be manufactured according to the methods similar to those of [Step 1-74].

[Step 1-78]

(2006) This step is a step wheein compound (16-71) is obtained by reducing compound (16-66). There are no particular imitations on the solvent used in this reaction as long as it discovers the starting materials to a certain extent without impeding the reaction. Exemples of the solvent include ether solvents such as tetrahydrofuran and diethyl ether; aromatic hydrocatron solvents such as benzene and follower and the like. Examples of the reducing agent include lithium aluminum hydride-aluminum-chloride. The lithium aluminum hydride is used in the aromatof 3 to 8 equivalents based on compound (16-66). The aluminum chloride is used in the enceint of 3 to 10 equivalents based on compound (16-66). The reaction temperature is from 0°C to refulx uncerneature, and the neaction time is from 10 minutes to 48 hours.

[Manufacturing Method 1-3-17] Method 2 of manufacturing compound (1 c-5):

[0207]

(wherein R3 and Q are defined as above.)

[0208] Compound (1c-69) can be manufactured from commercially available products by the well known methods, or compound (1c-69) can be manufactured according to the methods similar to those of [Step 1-76].

[Step 1-79]

[0209] This step is a step wherein compound (1c-72) is obtained by reducing compound (1 c-69). Compound (1 c-72)

can be manufactured according to the methods similar to those of [Step 1-78].

[Manufacturing Method 1-3-18] Method 1 for manufacturing compound (1c-6):

[0210]

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(wherein R3, R13 and R13 are defined as above.)

[0211] Compound (1c-42) can be manufactured from commercially available products by the well known methods, or compound (1c-42) can be manufactured according to the methods similar to those of [Step 1-56].

[Step 1-80]

[0212] This step is a step wherein compound (1c-73) is obtained by simultaneous reduction and acetal deprotection of compound (1c-42) using lodotrimethylsilane. There are no particular imitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include ether solvents such as tetrahydrofuran; acetonitrile, methylene chloride and the like, and preferably methylene chloride or acetonitrile. The lodotrimethylsilane is used in the amount of 2 to 10 equivalents based on compound (1c-42). The reaction temperature is from 0°C to 60°C, and the reaction time is from 5 minutes to 6 hours. The lodotrimethylsilane used in the reaction commay be a commercial product, or may be prepared at the time of use by reacting sodium iodide and chlororimethylsilane is acetoritized to come temperature.

30 Manufacturing Method 1-3-191 Method 2 for manufacturing compound (1c-6)

[0213]

(wherein R28 represent a halogen or a C1.6 alkyl group.)

[0214] Compound (1c-74) and compound (1c-74-1) which are commercially available products can be used as is, or they may be manufactured from commercially available products by the known methods.

[Step 1-81]

[0215] This step is a step wherein compound (1c-75) is obtained by reacting compound (1c-74) and compound (1c-74). In the presence of a base. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Exemples of the solvent include either solvents such as tetrahyrdrotruna and 1-4 dioxane, aromatic hydrocarbon solvents such as becare and toluene, smide solvents such as N-4 dimethyrformarnide and N-mathypyrrolidione, dimethylsufloxide, mixed solvents of the foregoing, or the like. Examples of the base include sodium hydride, potassium hydroxide, sodium hydroxide, potassium hydroxide, sodium bicarbonate, potassium carbonate or the like. Compound (1c-74) is used in the amount of 0.5 to 2 equivalents based on compound (1c-74-1). The base is used in the amount of 0.5 to 5 equivalents based on compound (1c-74-1). The reaction timepresture is from 100°C to 170°C, and the reaction time is from 30 minutes to 12 hours.

[Manufacturing Method 1-3-20] Method 3 for manufacturing compound (1c-6)

[0216]

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(wherein $\rm R^{29}$ and $\rm R^{30}$ represent a halogen, a $\rm C_{1-6}$ alkyl group and a $\rm C_{1-6}$ alkoxy group.)

[0217] Compound (1c-76), compound (1c-79) and compound (1c-76-1) which are commercially available products can be used as is, or they may be manufactured from commercially available products by the known methods.

Step 1-82]

[0218] This step is a step wherein compound (1c-77) is obtained by reacting compound (1c-78) and compound (1c-76), in the presence of a bas. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Exemples of the solvent include either solvents such as tetrahydrofuran and (1,4-dioxner; exematic hydrocarbon solvents such as benzene and toluene; amide solvents such as NV-dimethyformanide and N-methyfyprodidinone; dimethy sulfoxide, picked solvents of the foregoing, or the like. Examples of the base include sodium hydride, potassium t-butoxide, sodium hydroxide, potassium index objects of the amount of 10 c.2 equivalents based on compound (1c-76). The base is used in the amount of 2 to 3 equivalents based on compound (1c-76). The reaction temperature is form porom bennestature to 80°C, and the reaction in their point parties of minuses to 27 but only the product of the solution of the solution of minuses to 27 but only muster 50°C. and the reaction of their is form porom primities to 27 but only muster 50°C and the reaction in the inform 30°C minuses to 27 but only the solution of the solution of the solution of minuses to 27 but of the solution of the solution of minuses to 27 but of the solution of the solution of minuses to 27 but of the solution of the solution of minuses to 27 but of the solution of the solution of the solution of minuses to 27 but of the solution of the solution of minuses to 27 but of the solution of the so

[Step 1-83]

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[0219] This step is a step wherein compound (1c-78) is obtained by reducing the cyano group of compound (1c-77). Compound (1c-78) can be manufactured according to the methods similar to those of [Step 1-18].

[Step 1-84]

[0220] This step is a step wherein compound (1c-78) is obtained by reacting compound (1c-79) and compound (1c-76-1), in the presence of a base. Compound (1c-78) can be obtained according to the methods similar to those of [Step 1-82].

5 [Manufacturing Method 1-3-21] Method 4 for manufacturing compound (1c-6)

[0221]

(wherein R31 and R32 represent a halogen, a C1-6 alkyl group and a C1-6 alkoxy group.)

[0222] Compound (1c-80) and compound (1c-80-1) which are commercially available products can be used as is, or they may be manufactured from commercially available products by the known methods.

[Step 1-85]

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[0223] This step is a step wherein compound (1c-81) is obtained by reacting compound (1c-80) and compound (1c-80 of the solvent include acetic acid or the like. Compound (1c-80 -1) is unit in the amount of 1c equivalent based on compound (1c-80). The reaction temperature is from 50°C to 110°C, and the reaction time is from 5 minutes to 1 hours.

[Manufacturing Method 1-3-22] Method 5 for manufacturing compound (1c-6)

[0224]

(wherein R3 is defined as above.)

6 [0225] Compound (1c-82) and compound (1c-56-1) which are commercially available products can be used as is, or they may be manufactured from commercially available products by the known methods.

[Step 1-86]

[0226] This step is a step wherein compound (16-83) is obtained by carrying out a reductive amination of compound (16-82) and compound (16-56-1). Compound (16-83) can be manufactured according to the methods similar to those of (5tep 1-72).

[Step 1-87]

[0227] This step is a step wherein compound (1c-84) is obtained by deprotecting of acetal in compound (1c-83) by adding an acid. Compound (1c-84) can be manufactured according to the methods similar to those of [Step 1-16].

[Manufacturing Method 1-3-23] Method 6 for manufacturing compound (1c-6)

[0228]

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(wherein ring A and Hal are defined as above; R^{33} represents a $C_{1.6}$ alkyl group, a $C_{3.8}$ cycloalkyl group, a $C_{6.10}$ aryl group, or a 5- or 6-membered ring heteroaryl group, which may have 1 or 2 substituents selected from the substituent

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group α^1 , respectively; M+ represents a potassium cation and a sodium cation. (Substituent group α^1)

a cyano group, a C_{1,6} alk/y group, a C_{1,6} alkoy group, a C_{1,6} alkoycyarbonyl group and a C_{2,6} cycloaikyl group) [0229] Compound (1c-85,0 propound (1c-85,1) compound (1c-86-9) and compound (1c-85,0 propound (1c-85) and compound (1c-85) and a recomposing as a available products can be used as is, or they may also be manufactured from commercially available products by the known method.

[Step 1-88]

10 [0230] This step is a step wherein compound (1c-86) is obtained by reacting compound (1c-85) and compound (1c-85-1) or compound (1c-85-2), in the presence of a palladium catalyst and a base. An inorganic salt such as lithium chloride; an ammonium salt such as tetrabutylammonium chloride; or a phosphine ligand can also be added to obtain good results. This reaction can be carried out under an inert gas atmosphere, such as nitrogen gas and argon gas, There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include ether solvents such as 1,4-dioxane and tetrahydrofuran; aromatic hydrocarbon solvents such as toluene and xylene; amide solvents such as N,N-dimethylformamide and N-methylpyrrolidinone; dimethyl sulfoxide, water, mixed solvents of the foregoing, and the like. Examples of the palladium catalyst include palladium (II) acetate, tetrakis(triphenylphosphine)palladium (0), dichlorobis(triphenylphosphine)palladium (II) tris (dibenzylidene acetone)dipalladium (0), palladium carbon, bis(tri-t-butyl phosphine)palladium (0),1,1'-bis(diphenyl phosphinoferrocene)dichloro palladium (II), or the like. Examples of the phosphine ligand include triphenylphosphine, tri-o-tolylphosphine, tri-f-butylphosphine, tricyclohexyl phosphine, diphenylphosphinoferrocene, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-dif-butylphosphino-2',4',6'-triisopropylbiphenyl, 2-di-f-butylphosphinobiphenyl, 2-dicyclohexylphosphinobiphenyl, 2-dicyclohexylphosph clohexylphosphino-2'-(N, N-dimethylamino)biphenyl, 2-di-t-butylphosphino-2'-(N,N-dimethylamino)biphenyl, 2,2'-bis (diphenylphosphino)-1.1'-binaphthyl, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,4-bis (diphenylphosphino)butane, or the like, Examples of the base include potassium carbonate, sodium carbonate, cesium carbonate, potassium fluoride, cesium fluoride, potassium phosphate, sodium hydroxide, barium hydroxide, potassium hydroxide, or the like. Compound (1c-85-1) or compound (1c-85-2) is used in the amount of 1 to 3 equivalents based on compound (1c-85). The palladium catalyst is used in the amount of 0.01 to 0.25 equivalents based on compound (1c-85). The phosphine ligand is used in the amount of 0.01 to 1 equivalent based on compound (1c-85). Inorganic salts such as lithium chloride, or ammonium salts such as tetrabutylammonium chloride, are used in the amount of 0.5 to 2 equivalents. The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 10 minutes to 72 hours.

Step 1-89]

[0231] This step is a step wherein compound (1c-86) is obtained by reacting compound (1c-85) with compound (1c-85-3), under a palladium catalyst. An inorganic salt such as lithium chloride, an ammonium salt such as tetrabutylammonium chloride, a phosphine ligand, or a copper reagent can also be added to obtain good results. This reaction can be carried out under an inert gas atmosphere, such as nitrogen gas and argon gas. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include ether solvents such as 1,4-dioxane and tetrahydrofuran; aromatic hydrocarbon solvents such as toluene and xylene; amide solvents such as N.N-dimethyl formamide and N-methyl pyrrolidinone; dimethyl sulfoxide, mixed solvents of the foregoing, or the like. Examples of the palladium catalyst include palladium (II) acetate, tris (dibenzylideneacetone)dipalladium (0), dichlorobis(triphenylphosphine)palladium (II), dichlorobis(tri-o-tolylphosphine) palladium (II), bis(tri-t-butylphosphine)palladium (0), tetrakis(triphenylphosphine) palladium (0),1,1'-bis (diphenylphosphinoferrocene)dichloro palladium (II), or the like. Examples of the phosphine ligand include triphenylphosphine, tri-o-tolylphosphine, tri-t-butylphosphine, diphenylphosphinoferrocene, or the like, Examples of the copper reagent include copper (I) lodide, copper (I) bromide, copper (I) chloride, or the like. Compound (1c-85-3) is used in the amount of 1 to 3 equivalents based on compound (1c-85). The palladium catalyst is used in the amount of 0.01 to 0.25 equivalents based on compound (1c-85). The phosphine ligand is used in the amount of 0.01 to 1 equivalent based on compound (1c-85). The copper reagent is used in the amount of 0.1 to 3 equivalents based on compound (1c-85). Inorganic salt such as lithium chloride, or ammonium salt such as tetrabutylammonium chloride, are used in the amount of 0.5 to 2 equivalents. The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 10 minutes to 72 hours

[Manufacturing Method 1-3-24] Method for manufacturing compound (1c-85-2)

[0232]

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(wherein Hal and Hal' each independently represents a halogen atom; R²⁴ represents a C₁₋₆ alkyl group, a C₁₋₆ alkyl group, a C₁₋₆ alkyl group, a C₃₋₆ cycloalkyl group; M* represents a potassium cation and a so

and a solution 4:00th (1c-87), compound (1c-88-1), compound (1c-90) and compound (1c-91) which are commercially available products can be used as is, or they may be manufactured from commercially available products by the known methods. Compound (1c-91) which a commercially available product can be used as is, or may be manufactured from commercially available and the commercially available products by the known methods (for instance, WOQ005/033079 A1, a case 82-94, and the like).

[Step 1-90]

[0234] This step is a step wherein compound (1c-88) is manufactured by reacting an organometallic reagent and compound (1c-87) to generate an anionized compound, which is reacted with boric acid ester, then neutralizing the reaction mixture by the addition of an acid, and finally by reacting with a diol such as pinacol. This reaction can also be carried out by adding an organometallic reagent to a mixture of compound (1c-87) and boric acid ester, in which the generation of anion from compound (1c-87) and reacting with boric acid ester are occurred simultaneously. This reaction can also be carried out under an inert gas stream or atmosphere, such as nitrogen or argon. Examples of compound (1c-87) include chloroiodomethane, dibromo methane, bromoiodomethane, or the like, and preferably, chloroiodomethane and dibromo methane. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane, methyl-t-butyl ether, cyclopentyl methyl ether, diethyl ether, diisopropyl ether, dibutyl ether and dicyclopentyl ether; aromatic hydrocarbon solvents such as benzene and toluene; aliphatic hydrocarbon solvents such as heptane and hexane, mixed solvents of the foregoing, or the like, and preferably tetrahydrofuran. Examples of the boric acid ester include trimethyl borate, triisopropyl borate or the like, and preferably triisopropyl borate. Examples of the organometallic reagent include n-butyl lithium, s-butyl lithium and the like, and preferably n-butyl lithium. Examples of the acid include methanesulfonic acid, p-toluenesulfonic acid, hydrochloric acid-ethyl acetate solution, hydrochloric acid-methanol solution, or the like, and preferably methanesulfonic acid and hydrochloric acid-ethyl acetate solution. Boric acid ester can be used in the amount of 0.8 to 1.2 equivalents based on compound (1c-87); and preferably 0.9 to 1 equivalents. The organometallic reagent can be used in the amount of 0.8 to 1.2 equivalents based on compound (1c-87), and preferably 0.8 to 1 equivalents, A mixture of the anionized compound prepared at -78°C from compound (1c-87) and boric acid ester is stirred for 1 to 3 hours at the temperature mentioned below. This mixture is neutralized at the temperature mentioned below, then pinacol is added and stirred for 10 to 60 minutes at the temperature mentioned below.

[Reaction temperature during the reaction of anionized compound and boric acid ester]

50 [0235] The mixture of anionized compound and boric acid ester is stirred at 0°C to room temperature, and more preferably at room temperature. [Reaction temperature during neutralization reaction and reaction with diol]. [0236] The temperature during the neutralization reaction of the diol is from 20°C to room temperature, and more preferably 0°C. The temperature defir the addition of the diol is from 20°C to room temperature, and more preferably 0°C. The temperature after the addition of the diol is from 20°C to room temperature, and more preferably 0°C. The temperature after the addition of the diol is from 20°C to room temperature, and more preferably 0°C. The temperature after the addition of the diol is from 20°C to room temperature, and more preferably 0°C. The temperature after the addition of the diol is from 20°C to room temperature, and more preferably 0°C. The temperature after the addition of the diol is from 20°C to room temperature, and more preferably 0°C. The temperature after the addition of the diol is from 20°C to room temperature, and more preferably 0°C. The temperature after the addition of the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and the diol is from 20°C to room temperature, and 20°C to room temperatu

preferably from room temperature

(Step 1-91)

- [0237] This step is a step wherein anionized compound, generated by reacting compound (1c-88-1) with a base, is reacted with compound (1c-88), followed by reacting with a hydrogen fluoride salt (potassium hydrogen fluoride or sodium hydrogen fluoride) to obtain compound (1c-89). This step can also be carried out by adding a catalytic amount of iodine compound such as potassium iodide and tetrabutylammonium iodide. This reaction can also be carried out under an inert gas stream or atmosphere, such as nitrogen or argon. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction, Examples of the solvent include ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane, methyl-t-butyl ether, cyclopentyl methyl ether, diethyl ether, discoropyl ether, dibutyl ether and dicyclopentyl ether; aromatic hydrocarbon solvents such as benzene and toluene; amide solvents such as N,N-dimethylformamide and N-methylpyrrolidinone; dimethyl sulfoxide, mixed solvents of the foregoing, or the like, and preferably tetrahydrofuran or N.N-dimethylformamide. Examples of the 15 base include sodium hydride, potassium bis(trimethylsilyl)amide, potassium hydride, and preferably sodium hydride and potassium bis(trimethylsilyl)amide. Compound (1c-88-1) can be used in the amount of 1 to 5 equivalents based on compound (1c-88), and preferably 2 to 3 equivalents. The above-mentioned base can be used in the amount of 1 to 5 equivalents based on compound (1 c-88), and preferably 2 to 3 equivalents. The above-mentioned hydrogen fluoride salt can be used in the amount of 2 to 8 equivalents based on compound (1c-88), and preferably 3 to 5 equivalents. [0238] The reaction time for aniozation reaction of compound (1c-88-1) is, preferably from 30 to 60 minutes for stirring for at the temperature mentioned below, and after adding compound (1c-88) to the mixture, the reaction time is from 1 to 12 hours for stirring at the temperature mentioned below. After adding hydrogen fluoride salt to the reaction mixture. the reaction time is from 10 to 120 minutes for stirring at the temperature mentioned below.
- 25 [Reaction temperature during anionization reaction]

[0239] The temperature during addition of the base is from 0°C to room temperature, more preferably 0°C. The temperature after addition of the base is from 0°C to 70°C, more preferably from room temperature to 50°C.

30 [Reaction temperature during reaction of anionized compound and compound (1c-88)]

[0240] The temperature during addition of compound (1c-88) is from 0°C to room temperature, and more preferably 0°C. The temperature after addition of compound (1c-88) is from room temperature to 100°C, more preferably from room temperature to 70°C.

[Reaction temperature during addition of hydrogen fluoride salt]

[0241] The temperature during addition of the reagent is from 0°C to room temperature, and more preferably 0°C. The temperature after addition of the reagent is from 0°C to room temperature, and more preferably room temperature.

[Step 1-92]

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[0242] This step is a step wherein anionized compound generated by reacting an organometallic reagent and compound (1c-90) is reacted with boric acid ester, followed by reacting with a hydrogen fluoride salt (potassium hydrogen fluoride or sodium hydrogen fluoride, or the like) to obtain compound (1c-89). In this step, the reaction can be carried out in a solvent or using a large amount of compound (1c-90) as the solvent. In addition, this step can be carried out in the presence of a base. This step can be carried out according to the general methods, for instance, 5th Edition of Jikkenkagakukoza 18 (pages 20 to 23), Tetrahedron Letters, Vol. 24, No.31, pp. 3165-3168, and the like, This reaction can also be carried out under an inert gas stream or atmosphere, such as nitrogen or argon. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include alighatic hydrocarbon solvents such as heptane and hexane, or the like, Preferably, compound (1c-90) is used in large amount as a solvent. Examples of the organometallic reagent include t-butyl lithium, sec-butyl lithium, or the like, preferably sec-butyl lithium. Examples of the base include potassium t-butoxide, potassium sec-butoxide, potassium methoxide, or the like, preferably potassium t-butoxide. An organometallic reagent is added to a mixture of compound (1c-90) and solvent at -75 to -60°C (preferably -75 to -70°C), then the mixture is stirred for 5 to 30 minutes (preferably 5 to 10 minutes) at -20 to 0°C (preferably -10 to -5°C). Then, boric acid ester is added to the mixture at -75 to -70°C, the mixture is then stirred for 10 to 60 minutes (preferably 10 to 30 minutes) at 10°C to room temperature (preferably room temperature). Hydrogen fluoride salt is added to the mixture at 0 to 5°C,

water is then added at the same temperature, the reaction mixture is warmed to room temperature, to obtain compound (1c-89). Preferably, compound (1c-90) is used in solvent amount based on the organometallic reagent. The brase can be used in the amount of preferably 0.6 to 1 equivalents based on the organometalic reagent. The borie acid ester can be used in the amount of 1 to 2 equivalents based on the organometalic reagent, and preferably 1 to 1.8 equivalents. The above-mentioned hydrogen fluoride sait can be used in the amount of 3 to 10 equivalents based on the above-mentioned broth caid ester compound, and preferably 3 to 5 equivalents.

(Step 1-93)

(2243) This step is a step wherein anionized compound, generated by reacting a organometallic reagent with compound (16-91), reacted with a borie acid ester (triscopropy) borate, trimethyl borate, 2-teopropay-4.4,5.5 tetramethyl-1,3.2-doxaborotaine, or the like), followed by reacting with a hydrogen fluoride, and the like) to obtain compound (16-98). This reaction can also be carried out under an inner gas stream or atmosphere, such as introgen or argon. There are no perfulual rimitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as tetrahydrofuran, 12-dimethoxyethrame, methyl behuyl either, orderpriny insthyl either, diethyl either, discopropyl either, discopropyl either, discopropyl either, discopropyl either, discopropyl either, and preferably tetrahydrofuran. Examples of the above-mentioned organometallic reagent includer p-butyl lithium, sec-butyl lithium, methyl lithium or the like, preferably havily lithium, compound (16-98) can be obtained by the two methods described below. If it is difficult to carry out the reaction (i), such as the anion generated by reacting organometallic reagent includence and the carbon of the foreign organometallic reagent and the carbon of the solvent of the foreign organometallic reagent and the carbon of the solvent of the proposition of the solvent of the foreign organometallic reagent and compound (16-91) is unstable, reaction (iii) is preferred.

- (i) In a solvent, an organometallic reagent and compound (16-91) are stirred for 30 to 120 minutes (preferably -30 to 80 minutes) at -75 to -60°C (preferably -75 to -70°C). Then, boric acid ester is added to the mixture at -75 to -70°C, whereafter the mixture is stiffed for 10 to 120 minutes (preferably 20 to 80 minutes) at 0°C to room temperature (preferably 0 to 6°C). All yidrogen fluoride satt is added to the mixture at 0 to 6°C, water is then added at the same temperature, and the reaction mixture is warmed to room temperature, to obtain compound (16-89).
- (ii) In a solvent, an organometallic reagent is added to a mixture of a boric acid ester and compound (1c-89) at 75 to 5°C preferably 75 to 7°C), and stirred for 10 to 120 minutes (preferably 20 to 80 minutes) are 75 to 5°C (preferably 0 to 5°C). Hydrogen fluoride satt is added to the mixture at 0 to 5°C), whereafter water is added at the same temperature, and the reaction mixture is warmed to room temperature, to obtain compound (1-6).

[0244] The organometallic reagent can be used in the amount of 0.8 to 1.2 equivalents based on compound (10-91), and preferably 1 equivalent. The boric acid ester can be used in the amount of 1 to 2 equivalents based on compound (10-91), and preferably 1 to 1.2 equivalents. The hydrogen fluoride salt can be used in the amount of 3 to 10 equivalents based on compound (10-91), and preferably 3 to 5 equivalents.

[Manufacturing Method 2] Typical method for manufacturing compound (2a):

[0245]

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(wherein ring A, R1, R2, R3, R4 and Z are defined as above.)

[Manufacturing Method 2-1-1] Method 1 for manufacturing compound (2a):

5 [0246]

(wherein ring A. R1, R2, R3, R4 and Z are defined as above.)

[0247] Compound (2b) can be manufactured from commercially available products by the well known methods, or can also be manufactured according to the methods described in the Manufacturing Examples in the Examples, [Manufacturing Method 2-2-1] given below or the like.

[0248] Compound (2c) which is a commercially available product can be used as is, or compound (2c) can also be manufactured from excitable products by the well known methods. Compound (2c) can further be manufactured according to the methods described in the Manufacturing Examples in the Examples, [Manufacturing Method 2-31 driven below or the like.

[Step 2]

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[0249] This step is a step wherein compound (2a) is manufactured by reacting compound (2b) and compound (2b) in the presence of a base. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as tetrahydrofuran and diethyl either, aromatic hydrocarbon solvents such as benzene and toluene; amide solvents such as NN-dimethylformamide and N-methylyprofilione; alcohol solvents such as methanol and ethanol; and dimethyl sulfoxide, mixed solvents of the foregoing and like. Examples of the base include sodium hydride, potassium rbutoxide, sodium ethoxide, triethylamine, sodium hydroxide, potassium hydroxide and the like. Compound (2b) is used in the amount of 1 to 5 quivalents based on compound (2b). The base is used in the amount of 1 to 5 equivalents based on compound (2b). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 2b hours.

[Manufacturing Method 2-1-2] Method 2 for manufacturing compound (2a):

[0250]

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(wherein ring A, R1, R2, R3, Hal and Z are defined as above.)

[0251] Compound (1 b-1) which is a commercially available product can be used as is, or compound (1 b-1) can also be manufactured from commercially available products by the well known methods. Compound (2d) can be manufactured from commercially available products by the well known methods, or can be manufactured according to the methods described in the Manufacturing Exemples in the Examples, [Manufacturing Method 2-4] given below or the like.

5 (Step 2-11

[0252] This step is a step wherein compound (2a-1) is obtained by reacting compound (1 b-1) with compound (2d) in the presence of a calladium catalyst, Inorganic salts such as lithium chloride, ammonium salts such as tetrabutylammo-

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nium chloride, phosphine ligands, or copper reagents can be added to obtain good results. There are no particular illimitations on the solvent used in this reaction as long as it discolves the starting materiats to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as 1.4 dioxane and tertahydrofuran aromatic hydrocarbon solvents such as 1.0 the solvents such as 1.4 dioxane and tertahydrofuran aromatic hydrocarbon solvents such the solvents of the toregoing and the like. Examples of the palladium catalyst include palladium (ii) acetate, trist(chernylidenacetron)dipalladium (ii), dichlorosis(triphenylphosphine)palladium (iii) settler to hydrosphine)palladium (iiii) settler to hydrosphine)palladium (iii

[Manufacturing Method 2-1-3] Method 3 for manufacturing compound (2a)

[0253]

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(wherein ring A, Hal, L, R1, R2 and R33 are defined as above.)

[0254] Compound (2b-1) can be manufactured from commercially available products by the known methods, and can also be manufactured according to the methods described in the Manufacturing Example in Examples or [Manufacturing Method 2:2-1], and the like. Compound (2b-1) which is a commercially available product can be used as is, or may also be manufactured from commercially available products by the known methods. Compounds (1c-85-1), (1c-85-2) and (1c-85-3) which are commercially available products can be used as is, or may also be manufactured from commercially available products by the known methods.

40 [Step 2-2]

[0255] This step is a step wherein compound (2a-2) is obtained by reacting compound (2b-1) and compound (2c-1), in the presence of a base. Compound (2a-2) can be manufactured according to the methods similar to those of [Step 2].

45 [Step 2-3]

[0256] This step is a step wherein compound (2a-3) is obtained by reacting compound (1c-85-1) or compound (1c-85-2) and compound (2a-2), in the presence of a palladium catalyst and a base. Compound (2a-3) can be manufactured according to the methods similar to those of [Step 1-88].

[Step 2-4]

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[0257] This step is a step wherein compound (2a-3) is obtained by reacting compound (1c-85-3) and compound (2a-2), in the presence of a palladium catalyst. Compound (2a-3) can be manufactured according to the methods similar to 5 those of (5so 1-89).

[Manufacturing Method 2-2-1] Method 1 for manufacturing compound (2b):

[0258]

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[step2-6] [step2-6] [step2-6] [step2-6] [step2-6] [step2-6] [step2-7]

(wherein R1, R2 and Hal are defined as above.)

[0259] A commercially available product can be used as is for compound (2b-2). Compound (1b-1) which is a commercially available product can be used as is or compound (1b-1) can also be manufactured from commercially available products by the well known methods.

[Step 2-5]

[0260] This step is a step wherein compound (2b-2) is obtained by reacting compound (2b-2) with chlorotriphenyimethane in the presence of a base. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Exemples of the solvent include either solvents such as tetrahydrofuran and diefliry either, amide solvents such as Ni-Memethylomarmide and N-methylogirolidinone; and dimethyl sulfoxide, mixed solvents of the foreigning and the file. Exemples of the base include tristylamine, sodium hydride, potassium ibutoxide, potassium carbonate, sodium hydroxide and the like. The base is used in the amount of 1 to 4 equivalents based on compound (2b-2). The chlorotriphenylimethane is used in the amount of 1 to 4 soulvalents based on compound (2b-2). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 1 hour to 24 hours.

[Step 2-6]

[0261] This step is a step wherein compound (26-4) is obtained by reacting compound (26-3) with a boronic acid derivative in the presence of a palledium catalyst and a base. A phosphine ligand may also be added to obtain good results. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as 1/k-1/d-meth-ylformamide and N-methylpyrrolidinone; and directly sulfoxide, mixed solvents of the foregoing and the like. Examples of the pelladium catalyst include palladium (10, described, insidebarydelmaneceton-plainelfadium (0, disclinot/stripheryl-phosphine)palladium (0), the control stripheryl-phosphine)palladium (0), the control stripheryl-phosphine)palladium (0), the control of the control stripheryl-phosphine)palladium (0), the control stripheryl-phosphine)palladium (10, the control stripheryl-phosphine)palladium

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include bispiracolate/bitoron, 4.4,5.5, tetramethyl-[1,3,2] dioxaborolane and the like. Examples of the phosphine ligand include tripherylphosphine, thrisylchexylphosphine, dipherylphosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosphine/phosp

[0262] Compound (2b-4) can also be obtained from compound (2b-3) according to the method given below as Alternative Method (1).

- Alternative Method (1) Compound (2b-3) can be obtained by first anionizing the bromine atom of compound (2b-3) using an organometallic reagent, and then reacting with a boronic acid ester. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as betanhydrofuran and dethyl ether; aromatic hydrocarbon solvents such as benzenee and followers, and hexame, mixed solvents of the foregoing and the like. Examples of the organometallic reagent include n-butyl Rhium, a-butyl lithium, a-butyl lithium and the like. Examples of the boronic acid ester include 2-methoxy-4.6,5-tetramethyl-13,2-disoxaborolane, trimethyl borate, triiscopropy borate and the like. (1-friphery lime-thyl)-pyrazol-4-yl boronic acid, which is produced in the case of using trimethyl borate or thiscopropyl borate as the boronic acid ester, can be converted in the a boronic acid princed ester in accordance with the literature (Journal of Hetzrocyclic Chemistry, Vol. 4.1, No. 6, 931 to 939, so as to obtain compound (2b-3). The boronic acid ester is used in the amount of 1 to 1.5 equivalents based on compound (2b-3). The boronic acid ester is used in the amount of 1 to 1.5 equivalents based on compound (2b-3). The boronic acid ester is used in the amount of 1 to 1.5 equivalents based on compound (2b-3). The boronic acid ester is used in the amount of 1 to 1.5 equivalents based on compound (2b-3). The boronic acid ester is used in the amount of 1 to 1.5 equivalents based on compound (2b-3). The boronic acid ester is used in the amount of 1 to 1.5 equivalents based on compound (2b-3). The boronic acid ester is used in the amount of 1 to 1.5 equivalents based on compound (2b-3). The boronic acid ester is used in the amount of 1 to 1.5 equivalents because on compound (2b-3). The boronic acid ester is used in the amount of 1 to 1.5 equivalents because on compound (2b-3). The portion acid ester
- [0263] Note that (1-triphenylmethyl)-pyrazol-4-yl boronic acid, which is produced in the case of using trimethyl borate or triisopropyl borate as the boronic acid ester in this reaction, can be used in place of compound (2b-4) as the substrate in IStep 2-7I.

[Step 2-7]

[0264] This step is a step wherein compound (2b-5) is obtained by reacting compound (2b-4) with compound (1b-1) in the presence of a palladium catalyst and a base. A phosphine ligand can be added to obtain good results. A quaternary ammonium salt such as tetrabutylammonium bromide, tetrabutylammonium chloride and the like can also be added in the amount of 0.1 to 2 equivalents based on compound (2b-4). There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include ether solvents such as 1,4-dioxane and tetrahydrofuran; aromatic hydrocarbon solvents such as benzene and toluene; amide solvents such as N,N-dimethylformamide and N-methylpyrrolidinone; alcohol solvents such as methanol and ethanol; and dimethyl sulfoxide, water, mixed solvents of the foregoing and the like. Examples of the palladium catalyst include palladium (II) acetate, tris(dibenzylidenacetone)dipalladium (0), dichlorobis(triphenylphosphine)palladium (II), bis(tri-t-butylphosphine)palladium (0), tetrakis(triphenylphosphine)palladium (0), 1,1'-bis(diphenylphosphinoferrocene)dichloropalladium (II) and the like. Examples of the base include sodium carbonate, potassium carbonate, cesium carbonate, cesium fluoride, potassium phosphate, sodium hydroxide, potassium hydroxide and the like. Examples of the phosphine ligand include triphenylphosphine, tri-t-butylphosphine, tricyclohexylphosphine, diphenylphosphinoferrocene, 2-dicyclohexylphosphinobiphenyl and the like. The palladium catalyst is used in the amount of 0.01 to 0.3 equivalents based on compound (2b-4). The base is used in the amount of 1.5 to 10 equivalents based on compound (2b-4). Compound (1b-1) is used in the amount of 1.0 to 3.0 equivalents based on compound (2b-4). The phosphine ligand is used in the amount of 0.01 to 1.2 equivalents based on compound (2b-4). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 10 minutes to 24 hours.

[Step 2-8]

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[0265] This step is a step wherein compound (2b-1) is obtained by deprotecting the triphenylmethyl group of compound (2b-5) under addic conditions. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Example of the solvent include ether solvents such as 1.4-dioxane and tetrahydrofuran; aromatic hydrocarbon solvents such as benzene and to luene, a cohol solvents such as methanol and ethanol; methylene chloride, water, mixed solvents of the foregoing and the fike. Examples of the add include hydrochrionic acid, suffuring acid, hydrothomic acid, throuncasetic acid, formic acid and the Ric. The acid is used in the amounts of from 2 equivalents to the solvent amount based on compound (2b-5). The reaction temperature is from 0°C to reflux removalence, and the reaction time is from 10°C integers to 24 hours.

[Manufacturing Method 2-2-2] Method 2 for manufacturing compound (2b)

[0266]

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(wherein R1, R2 and Hal are defined as above.)

[0267] Compound (2b-6) which is a commercially available product can be used as is, or may be manufactured from commercially available products by the known methods. Compound (2b-4) can be manufactured according to the methods described in [Manufacturing the thot 2-2-1].

[Step 2-9]

[0268] This step is a step wherein compound (2b-7) is obtained by substituting a halogen atom for a hydrogen atom on the pyridine ring of compound (2b-6). Compound (2b-7) can be manufactured according to the methods similar to those of [Step 1-11].

[Step 2-10]

[0269] This step is a step wherein compound (2b-8) is obtained by reacting compound (2b-7) with compound (2b-4), in the presence of a palladium catalyst and a base. Compound (2b-8) can be manufactured according to the methods similar to those of [5tep 2-7]. With the proviso that compound (2b-4) is used in the amount of 1 to 1.2 equivalents based on compound (2b-7).

[Step 2-11]

[0270] This step is a step wherein compound (2b-9) is obtained by deprotecting the triphenyl methyl group of compound (2b-8) under acidic conditions. Compound (2b-9) us be manufactured according to the methods similar to those of [Step 2-8], [Manufacturing Method 2-3] Method for manufacturing compound (2b):

(wherein ring A, L, R3 and Z are defined as above.)

[0271] Compound (1c-3) which is a commercially available product can be used as is, or compound (1c-3) can also be manufactured from commercially available products by the well known methods. Compound (1c-3) can further be manufactured according to the methods described in the Manufacturing Examples in the Examples, [Manufacturing Method 1:3-1] given above or the like.

5 [Step 2-12]

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[0272] This step is a step wherein compound (2c) is obtained by converting the hydroxyl group of compound (1c·3) into a leaving group. Compound (2c) can be manufactured according to the methods similar to those of [Step 1-32].

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[Manufacturing Method 2-4] Method for manufacturing compound (2d):

[0273]

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(wherein ring A, L, R3 and Z are defined as above.)

[0274] Compound (2c) which is a commercially available product can be used as is, or compound (2c) can also be manufactured from commercially available products by the well known methods. Compound (2c) can unfurter be manufactured according to the methods described in the Manufacturing Examples in the Examples, [Manufacturing Method 2-3] cives above or the like. A commercial product may be used as is for compound (2b-2r).

20 [Step 2-13]

[0275] This step is a step wherein compound (2d-1) is obtained by reacting compound (2c) with compound (2b-2). Compound (2d-1) can be manufactured according to the methods similar to those of [Step 2].

25 [Step 2-14]

[0278] This stop is a stop wherein compound (20) is obtained by reacting compound (20-1) with hexa(r-buly)drift in the presence of a palladium catalyst. A phosphine (igand can be added into this reaction in order to obtain good results. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include other solvents such as 1,4-0-daxona and tetrahydrotrurs, aromatic hydrocarbon solvents such as and sylence; andes solvents such as 1,8-0-dimethylor-maminde and N-methylgyprotidinone; dimethyl sulfoxide, mixed solvents of the foregoing and the like. Examples of the palladium catalyst include palladium (II) actals, this (disbenz)dienaectone)dipalladium (II), dichlorobis(trib-orty)phosphine)palladium (III), dichlorobis(trib-orty)phosphine)palladium (III), dichlorobis(trib-orty)phosphine)palladium (III), dichlorobis(trib-orty)phosphine)palladium (III), dichlorobis(trib-orty)phosphine)palladium (III), dichlorobis(trib-orty)phosphine)phosphine and the IIIs. The hexa(r-bury)dith is used in the amount of 1 to 10 equivalents, perferably 3 to 5 equivalents, based on compound (2d-1). The palladium catalyst is used in the amount of 1 to 10 equivalents based on compound (2d-1). The phosphine ligand is used in the amount of 1 to 2 equivalents based on compound (2d-1). The phosphine ligand is used in the amount of 1 to 10 equivalents based on compound (2d-1). The phosphine ligand is used in the amount of 1 to 10 equivalents based on compound (2d-1). The phosphine ligand is used in the amount of 1 to 10 equivalents based on compound (2d-1). The phosphine ligand is used in the amount of 1 to 10 equivalents based on compound (2d-1). The phosphine ligand is used in the amount of 1 to 10 equivalents based on compound (2d-1). The phosphine ligand is used in the amount of 1 to 10 equivalents based on compound (2d-1). The phosphine ligand is used in the amount of 1 to 10 equivalents based on compound (

10277] Compound (2d) can also be obtained from compound (2d-1) according to the method given below as Alternative Method (1). Atternative Method (1). Atternative Method (1). Compound (2d-2) can be obtained by first anionizing the bornine stoom of compound (2d-1) using an organometalito reagent, and then reacting with tri(n-buty)tin ohioride. There are no particular limitations on the solvent used in this reaction as born one as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as the high properties of the organometrial reagent include about the starting through the solvents of the foregoing and the like. Examples of the organometallor exagent include arbust lithium, a buty lithium, a buty lithium, a buty lithium and the like. The organometallor reagent is used in the amount of 1 to 1.5 equivalents based on compound (2d-1). The reaction temperature for the anionization reaction is from -90°C to -60°C, with a reaction time being from 10 minutes to 12 hours. The temperature for the reaction with the tri(n-buty)tin chloride is from -70°C to 0°C, with a reaction time being from 10 minutes to 12 hours.

[Manufacturing Method 3] Typical method for manufacturing compound (3a):

[0278]

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(wherein ring A, R1, R2, R3 and Z are defined as above.)

[Manufacturing Method 3-1] Method for manufacturing compound (3a):

[0279]

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$$(bb) \qquad (bc) \qquad$$

(wherein ring A, R¹, R², R³ and Z are defined as above.)

[0280] Compound (3b) can be manufactured from commercially available products by the well known methods, or compound (3b) can also be manufactured according to the methods given in the Manufacturing Examples in the Examples, [Manufacturing Method 3-2] given below or the like.

[0281] Compound (3c) can be manufactured from a commercially available product by the well known methods, or compound (3c) can also be manufactured according to the methods given in the Manufacturing Examples in the Examples, [Manufacturing Method 3-3] given below or the like.

(Step 3)

35 [0282] This step is a step wherein compound (3a) is obtained by reacting compound (3b) with compound (3c). Compound (3a) can be manufactured according to the methods similar to those of [Step 1-8].

[Manufacturing Method 3-2] Method for manufacturing compound (3b):

40 [0283]

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$$\bigcap_{\{Q_{2}^{(1)},\dots,Q_{n}^{(2)}\}} \bigcap_{\{2b=1\}}^{B_{1}} \bigcap_{\{2b=2,1\}} \bigcap_{\{q_{1}^{(1)},\dots,q_{n}^{(2)}\}} \bigcap_{\{b=1,2,2\}}^{B_{1}} \bigcap_{\{b=1,2,2\}} \bigcap_{\{a_{1}^{(1)},\dots,a_{n}^{(2)}\}} \bigcap_{\{b=1,2,2,2\}} \bigcap_{\{a_{1}^{(1)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)}\}} \bigcap_{\{a_{1}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)}\}} \bigcap_{\{a_{1}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n}^{(2)},\dots,a_{n$$

(wherein R¹ and R² are defined as above, and R^{2a} represents a hydrogen atom and - NHR^{2b}. R^{2b} represents a protective group such as 1-butoxycarbonyl, 1-butylcarbonyl and the like.)

[0284] Compound (3b-1) which is a commercially available product can be used as is, or compound (3b-1) can also be manufactured from commercially available products by the well known methods. A commercial product can be used as is for compound (2b-1).

[Step 3-1]

[0285] This step is a step wherein compound (3b-2) is obtained by reacting compound (3b-1) with compound (2b-1)

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in the presence of a base and a copper catalyst. A copper figand can also be added to improve the yield. There are no particular limitations on the solvent used in this reaction as long as it discovers the starting materials to a certain cetent without impeding the reaction. Exemples of the solvent include other solvents such as 1.4-dioxane and terrehydrofurary, aromatic hydrocarbon solvents such as benzene, toluene and xylene; amide solvents such as N.N-dimethydromemide and V-methylgryroridinone; and dimethyl sulfoxide, mixed solvents of the foregoing and the like. Exemples of the base used in this reaction include potassium carbonate, cestium carbonate, potassium phosphate, potassium rhoutoxide, copper (i) broinds and the like. Exemples of the copper catalyst include copper (i) broinds on the like. Exemples of the copper figand include 1,2-cyclohexanediamine, N,N-dimethyl-cyclohexaned-1,2-diamine, 1,10-phenanthroline and the like. Carbonator (2b-1). The copper diamine in the amount of 0.01 to 3.03 equivalents based on compound (3b-1). The copper catalyst is used in the amount of 1 to 3 equivalents based on the compound (3b-1). The copper catalyst is used in the amount of 1 to 3 equivalents based on compound (3b-1). The copper diamine is the solvent of 1 to 3 equivalents based on the copper catalyst.

15 [Step 3-2]

(0286) This step is a step wherein compound (3b) is obtained by reacting acid with compound (3b-2), so as to deproted an amine moiety. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include accords colvents such as methanol and ethanol; and water, mixed solvents to the foregoing and the like. Examples of the acid include inorganic acids such as tyridrochoric acid, suffusion existing acid, and hydrobromic acid; organic acids such as tyridrochoric acid; autification and include the amounts of from 2 equivalents to the solvent amount based on compound (3b-2). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 30 minutes to 72 hours.

[Manufacturing Method 3-3] Method for manufacturing compound (3c):

[0287]

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(wherein ring A, L, R3 and Z are defined as above.)

[0288] Compound (2c) can be manufactured from commercially available products by the well known methods, or compound (2c) can also be manufactured according to the methods described in the Manufacturing Examples in the Examples, [Manufacturing Method 2-3] given above or the like.

[Step 3-3]

1028] This step is a step wherein compound (3c) is obtained by reacting compound (2c) with tribuytin-anions. There are no particular initiations on the solvent used in this reaction as long as it dissolves the starting materials to a certain exent without impeding the reaction. Examples of the solvent include either solvents such as lettarly drout an and detryl ester, aromatic hydrocarbon solvents such as benzenes, lottened and yellowers include solvents of the foregoing and the like. The tributyth-anions used in the reaction can be synthesized by reacting an organometalic reagent with tributytin hydride. Examples of the organometalic reagent include lithium disopropylamide, isopropyl magnesium chief or organometalic reagent and organometalic reagent mount of 1 to 2 equivalents based on compound (2c). The organometalic reagent is used in the amount of 1 to 2 equivalents based on thibutytin hydride. The reaction empretature is from 10'minutes to 12 hours.

[Manufacturing Method 4] Typical method for manufacturing compound (4a):

[0290]

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(wherein ring A, R2, R3 and Z are defined as above.)

[Manufacturing Method 4-1] Method for manufacturing compound (4a):

[0291]

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(wherein ring A, R³ and Z are defined as above.)

[0292] Compound (4a-1) can be manufactured from commercially available products by the well known method, or compound (4a-1) can be manufactured according to the methods described in the Manufacturing Examples In the Examples (Nanufacturing Method 4-2) given below or the like.

90 [Step 4]

[0293] This step is a step wherein compound (4a) is obtained by substituting a hydrogen atom for a chlorine atom of compound (4a-1). Compound (4a) can be obtained by reacting compound (4a-1) in the presence of a palladium catalyst. a base and a hydrogen source. A phosphine ligand can also be added to obtain good results: There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include ether solvents such as 1,4-dioxane and tetrahydrofuran; aromatic hydrocarbon solvents such as toluene and xylene; amide solvents such as N,N-dimethylformamide and N-methylpyrrolidinone; and dimethyl sulfoxide, mixed solvents of the foregoing and the like. Examples of the palladium catalyst include bis(tri-t-butylphosphine)palladium (0), palladium (II) acetate, tetrakis(triphenylphosphine)palladium (0), dichlorobis (triphenylphosphine)palladium (II), tris(dibenzylidenacetone)dipalladium (0) and the like. Examples of the base include triethylamine, N,N-diisopropylethylamine and the like. Examples of the hydrogen source include formic acid, potassium formate, sodium formate, lithium formate, ammonium formate and the like. Examples of the phosphine ligand include triphenylphosphine, tri-o-tolylphosphine, tri-t-butylphosphine and the like. The palladium catalyst is used in the amount of 0.01 to 0.3 equivalents based on compound (4a-1). The base is used in the amount of 2 to 5 equivalents based on compound (4a-1). The hydrogen source is used in the amount of 1 to 5 equivalents based on compound (4a-1). The phosphine ligand is used in the amount of 0.01 to 1.2 equivalents based on compound (4a-1). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 30 minutes to 24 hours.

[Manufacturing Method 4-2] Method for manufacturing compound (4a-1):

[0294]

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(wherein ring A. R3 and Z are as defined above.)

[0295] Compound (4b) which is a commercially available product can be used as is. Compound (4c) can be manutfactured from conflict products by the well known methods, or compound (4c) can also be manufactured according to the methods described in the Manufacturing Examples in the Examples, [Manufacturing Method 4-3] given hollow or the like:

(Step 4-1)

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[0296] This step is a step wherein compound (4b-2) is obtained by reacting compound (4b-1) with hydroxylamine or hydroxylamine by hydroxylamine by hydroxylamine by hydroxylamine by hydroxylamine by particular imitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Exemples of the solvent include actional solvents such as methanol and ethanol; and methylam exhibited, water and the like. The base an also be used as the solvent. Examples of the base include pyridine, sodium hydroxylamine hydroxylam

[Step 4-2]

[0297] This step is a step wherein compound (4b-3) is obtained by reacting compound (4b-2) with a chlorinating agent. There are no particular inhitations on the solvent used in this reaction as long as it dissolves the starting materials to a cortain extent without tripeding the reaction. Exemples of the solvent include ether solvents such as I Advisore and tarrahydrofuran; alcohol solvents such as methanol and ethanol, amide solvents such as N.N-dimethylformamide and N-methylpyrorolidinone; and dimethyl sulfoxide, methylene chlorine, water, mixed solvents of the foregoing and the like. Examples of the chlorinating agent include N-chlorosuccinimide, sodium hypochlorite, chlorine and the like. The chlorinating agent is used in the amount of 2 to 5 equivalents based on compound (4b-2). The reaction temperature is from 0°C to room temperature, and the reaction time is from 10 minutes to 2 4 hours.

60 [Step 4-3]

[0298] This step is a step wherein compound (4a-1) is obtained by reacting compound (4b-3) with compound (4c). Compound (4a-1) can be manufactured according to the methods similar to those of [Step 1].

65 [Manufacturing Method 4-3] Method for manufacturing compound (4c):

[0299]

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(wherein ring A, R3, R5, R6, L and Z are defined as above.)

[0300] Compound (2c) can be manufactured from commercially available products by the well known methods, or

compound (2c) can also be manufactured according to the methods described in the Manufacturing Examples in the Examples, [Manufacturing Method 2-3] given below or the like.

[Step 4-4]

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[0301] This step is a step wherein compound (4c-1) is obtained by reacting compound (2c) with an ethyrylsilane derivative. Compound (4c-1) can be obtained by reacting compound (2c) with an ethyryl diagnet reagent obtained by reacting an ethyryl silane derivative with a Grignard reagent. A copper reagent such as copper (i) bromide, copper (i) iddie and the like can also be added to obtain good results. Examples of the ethyrylsilane derivative include frimethylsilyl acetylene, including the properties of the ethyrylsilane derivative include frimethylsilyl acetylene, the properties of the ethyrylsilane derivative and the like. An alkyl magnesium halide such as ethyl magnesium bromide and isopropyl magnesium chloride can be used as the Grignard reagent. The ethyrylsilane derivative can be used in the amount of 1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The copper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on compound (2c). The opper reagent can be used in the amount of 0.1 to 3 equivalents based on com

[Step 4-5]

[0302] This step is a step wherein compound (4c) is obtained by deprotecting the trimethylsityl group of compound (4c-1). Compound (4c) can be manufactured according to the methods similar to those of [Step 1-2].

[Manufacturing Method 5] Typical method for manufacturing compound (5a):

[0303]

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R⁴ (5a)

(wherein R1, R2, R3, R4, X and Y are defined as above.)

35 [Manufacturing Method 5-1] Method for manufacturing compound (5a):

[0304]

(wherein R1, R2, R3, R4, X and Y are defined as above.)

[0305] Compound (5s-1) can be manufactured according to the method described in the Manufacturing Examples in the Examples, (India-turing Method 5-2) given below on the like. Compound (1c-10-1) and compound (1c-10-2) which are commercially available products can be used as is, or they can also be manufactured from commercially available products by the velocities of velocities of the vel

[Step 5-1]

[0306] This step is a step wherein compound (5a) is obtained by adding 1 equivalent of base to compound (5a-1) to

obtain phenoxide ions, followed by reacting with compound (1c-10-2).

[0007] Phenoxide ion production: Phenoxide ions can be obtained by adding I equivalent of a base to compound (5e) in a solvent such as tetrahydrotiuran or methanol. Examples of the base include potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, potassium rbutoxide and the like, preferably sodium hydroxide. The solvent is preferably concentrated for use in the following reaction. The reaction tense from 5 minutes or to hour reaction time is from 5 minutes or to hour.

D300 Reaction of phenoxide ions with compound (1o-10-2): The phenoxide ions and compound (1o-10-2) are reacted in a solvent to obtain compound (5a). There are no particular imitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Exemple of the solvent include emide solvents such as N,N-dimetrylrormanide, N-methylpymolidinone and hexametrylyhosphoramide; and dimethyl sulfoxide, mixed solvents of the foregoing and the like. Compound (1o-10-2) used in the amount of 1 to 3 equivalents based on compound (5a-1). The reaction temperature is from room temperature to reflux temperature, and the reaction time form 10 minimum to 4A hours.

[0309] Compound (5a) can also be obtained from compound (5a-1) according to the method described below as Alternative Method (1).

Asternative Method (1): Compound (5a) can be obtained by reacting compound (5a-1) with compound (1o-1o-2) in the presence of a base. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materias to a cortain extent without impeding the reaction. Exemples of the solvent include either solvents such as tertarylyrofruran and diethyl either, aromatic hydrocarbon solvents such as benzene and toluene, amide solvents such as IN-dimethyllyromamide and N-methylpyrrofictioner, and dimethyl suikoride, mixed solvents of the foregoing and the like. Examples of the base include sodium hydride, potassium carbonate, sodium carbonate, cesium carbonate, potassium hydroxide, sodium hydroxide and the like. A catalytic amount of sodium lodide or potassium lodide or tetrabulyiammonium lodide can also be added to obtain good results. The base is added in the amount of 1 to 1.5 equilvalents based on compound (5a-1). The reaction temperature is from room temperature to reflux temperature, and the reaction time is from 10 minutes to 48 hours.

[Step 5-2]

[0310] This step is a step wherein compound (5a) is obtained by reacting compound (5a-1) with compound (1c-10-1).

Compound (5a) can be manufactured according to the methods similar to those of [Step 1-37].

[Manufacturing Method 5-2] Method for manufacturing compound (5a-1):

[0311]

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(wherein R1, R2, R4, X and Y are defined as above.)

[0312] Compound (5a-2) can be manufactured according to the methods described in the Manufacturing Examples in the Examples, [Manufacturing Method 1], [Manufacturing Method 2], [Manufacturing Method 3] and [Manufacturing Method 4] which are given above or the like.

[Step 5-3]

[0313] This step is a step wherein compound (5e-1) is obtained by reacting add with compound (5b-2). An additive such as thioanisole may be added in the reaction system to obtain better results. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as diethyl either and tetrahydrofuran; and methylene chloride, trifluoroacetic acid and the like. Examples of the acid include organic acids such as trifluoroacetic acid and methanesulfonic acid; inorganic acids such as sulturic acid; Lewis acids such as born trifluoride diethyl eitherate; and the like. Examples of the additives include thioanisole, eithenethiol, di-methonine and the like. The acid is used in the amount of 1 equivalent to the solvent amount based on compound (5e-2). The additive used in the amount of 1 to 5

equivalents based on compound (5a-2). The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 72 hours.

[0314] Compound (5a-1) can also be obtained from compound (5a-2) according to the method described below as Alternative Method (1).

Alternative Method (1): Compound (5a-1) can be obtained by reacting compound (5a-2) with boron tribromide or boron trichloride. There are no particular limitations on the solvent used in this reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction, but methylene chloride is preferably used. The boron tribromide or boron trichloride is used in the amount of 1 to 5 equivalents based on compound (5a-2). The reaction temperature is from -78°C to room temperature, and the reaction time is from 30 minutes to 24 hours.

[Manufacturing Method 6-1] Method 1 for manufacturing halogen-modified product of compound (1 a)

[0315]

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25 (wherein ring A, Z, Hal, R¹ and R³ are defined as above; R³9 represents a hydrogen atom or a C₁. 6 alkyl group.)
103161 Compound (6a-2) can be manufactured according to the methods described in [Manufacturing Method 1].

(Step 6-1)

[0317] This step is a step wherein compound (6a-1) is obtained by substituting a halogen atom for a hydrogen atom on the pyridine fing of compound (6a-2). Compound (6a-1) can be manufactured according to the methods similar to those of (Step 1-11).

[Manufacturing Method 6-2] Method 2 for manufacturing halogen-modified product of compound (1a)

[0318]

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(wherein ring A, Z, Hal, R² and R³ are defined as above; R⁴⁰ represents a hydrogen atom or a C₁₋₆ 6 alkyl group.) [0319] Compound (6a-4) can be manufactured according to the methods described in [Manufacturing Method 1].

[Step 6-2]

[0320] This step is a step wherein compound (6a-3) is obtained by substituting a halogen atom for a hydrogen atom on the pyridine ring of compound (6a-4). Compound (6a-3) can be manufactured according to the methods similar to those of (15tep 1-11).

[Manufacturing Method 7] Method 3 for manufacturing halogen-modified product of compound (1a)

[0321]

(wherein ring A, Hal, R3, R5, R6 and Z is defined as above.)

[0322] Compound (7a-1) which is a commercially available can be used as is. Compound (1c-1) can be manufactured from commercially available products by the known methods, and can be manufactured according to the methods described in Manufacturing Example of Example or [Manufacturing Method 1-3-1], and the like.

(Step 7-1)

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[0323] This step is a step wherein compound (7a-2) is obtained by substituting a halogen atom for a hydrogen atom on the pyridine ring of compound (7a-1). Compound (7a-2) can be manufactured according to the methods similar to those of [Step 1-11].

[Step 7-2]

[0324] This step is a step wherein compound (7a-3) is obtained by reacting compound (7a-2) and an ethinylsilane derivative. Compound (7a-3) can be manufactured according to the methods similar to those of [Step 1-1].

[Step 7-3]

[0325] This step is a step wherein compound (7a-4) is obtained by reacting compound (7a-3) with a base. Compound (7a-4) can be manufactured according to the methods similar to those of [Step 1-2].

[Step 7-4]

[0326] This step is a step wherein compound (7a) is obtained by reacting compound (7a-4) and compound (1c-1), in the presence of a base. Compound (7a) can be manufactured according to the methods similar to those of [Step 1].

[Manufacturing Method 8] Method 1 for manufacturing amino group-modified product of compound (1 a)

[0327]

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(wherein ring A, R², R³, R⁴, X, Y and Z are defined as above; R³ represents a hydrogen atom, a C_{1.5} alkyl group, a hydroxy C₁₋₅ alkyl group, a C₁₋₆ alkoxy carbonyl group or a C₁₋₆ alkoxy C₁₋₅ alkyl group.)

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[0328] Compound (8a-1-1) which is a commercially available product can be used as is, or may also be manufactured from commercially available products by the known methods. Compound (8a-1) can be manufactured according to the methods described in Manufacturing Method 11, or the like.

[Step 8]

[0329] This stop is a stop wherein compound (8a) is obtained by reacting compound (8a-1) and compound (8a-1) in the presence of a reducing agent. This stop can be carried out by adding an acid such as acetic acid or hydrochloric acid in catalytic amount to solvent amount. There are no particular limitations on the solvent used in this reaction as ong as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include other solvents such as tetrahydroturan and disthyl other; aromatic hydrocarbon solvents such as benzene and touency articles solvents such as NN-4-dimethylformamide and N-methylgymotionione; alcohol solvents such as methane and ethanol; hadgeneated hydrocarbon solvents such as methylane chloride and chlorionine, 2-dichlorioniane, water, acetic acid, mixed solvents of the foregoing, or the like, preferably a mix of solvent of NN-dimethylformamide and acetic acid. Examples of the reducing agent used in this reaction include or piclotine borane, softland-porane, sodium cyanoborhydride, sodium triacetoxylorohydride and the like, preferably expication borane. Compound (8a-1-1) can be used in the amount of 1 to 5 equivalents based on compound (8a-1-1) preferably 1 to 1.5 equivalents lang agent can be used in the amount of 10.5 to 5 equivalents the acet of the reaction in generature is from 0°C to reflux interveneurure. And the reaction lines is from 10 mixed to 48 hours.

[Manufacturing Method 9] Method 2 for manufacturing amino group-modified product of compound (1a)

[0330]

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(wherein ring A, R² , R³, R⁴, X, Y and Z are defined as above; R³ represents a $C_1 - 6$ alkyl group or a C_{1-6} alkoxyalkyl group.)

[0331] Compound (8a-1-2), compound (8a-1-3) and compound (8a-1-4) which are commercially available products can beused as is, or they may also be manufactured from commercially available products by the known methods. Compound (8a-1) can be manufactured according to the methods described in [Manufacturing Method 1], or the like.

[Step 9-1]

[0332] This stop is a stop wherein compound (8a) is obtained by reacting compound (8a)-12) or compound (8a)-12 with compound (8a) in the presence of a base. There are no particular imitations on the solvent used in its reaction as long as it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include either solvents such as tetrahydrofuran and diethyl either; aromatic hydrocarbon solvents such as the activity of the solvent in the solvents such as the solvents such as metrifyers either solvents such as nethylene chiloride and chloroform, mixed solvents of the foregoing, or the like. Examples of the base include such as the solvent in the solvents of the

[Step 9-2]

[0333] This step is a step wherein compound (8a is obtained by reacting compound (8a i-1) and it dissolves the starting materials to a certain extent without impeding the reaction. Examples of the solvent include halogenated hydrocachers such as such as Na-indentifyl marmide and An emethylyeroldnone; sufficiely desolvents such as distribution and i 1.4-dioxane; amide solvents such as ethyl acetate, mixed solvents of the foregoing, or the like. Examples of the condensing reagent include Bop (1 H-1,2-5-heartzaizel-1-yloxyfirdmethylaminip) hosphonium hexallworphosphate). WSC (1 ethyls-13-dimethylaminipopropi)carbodimide bydrochloride), DCC (N.N-dicyclohexylcarbodimide) for like. A catalytic amount of 4-dimethylaminipopyridine can also be added to accelerate the reaction. In addition, this step can also be carried out by adding a base such as triethylamine in the amount of 1 to 3 equivalents based on compound (8a-1), preferably 1 to 1.5 equivalents. Compound (8a-1) equivalents. The condensing reagent can be used in the amount of 1 to 3 equivalents based on compound (8a-1), preferably 1 to 1.5 equivalents. The reaction temperature is from 0°C to reflux temperature, and the reaction time is from 10 minutes to 48 hours.

[Manufacturing Method 10] Method 3 for manufacturing amino group-modified product of compound (1 a)

20 [0334]

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(wherein ring A, $\rm R^3$, $\rm R^4$, X, Y and Z are defined as above; $\rm R^{37}$ represents a hydrogen atom, a halogen atom, $\rm R^{12}$. (CO)-NH- $\rm R^{12}$ is a $\rm C_{16}$ alklyl group or a $\rm C_{16}$ alkoy $\rm C_{16}$ alklyl group, a C₁₆ alklyl group.

[0335] Compound (10a-1-1) which is be a commercially available product can be used as is, or may also be manufactured from the commercially available products by the known methods. Compound (10a-1) can be manufactured according to the methods described in [Manufacturing Method 1], or the like.

[Step 10]

[0336] This step is a step wherein compound (10a) is obtained by reacting compound (10a-1) and compound (10a-1) in the presence of a reducing agent. Compound (10a) can be manufactured according to the methods similar to 5 those of (Sign 8).

[Examples]

[0337] The compounds according to the present invention can be manufactured, for example, according to the methods described in the following manufacturing examples and examples. These are only examples, however, and the compounds according to the present invention are in no way limited to the following specific examples.

[Example 1] 3-(3-(4-Benzyloxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

55 [0338]

[0339] To a mixture of 4-benzyloxy phenyl-acetohydroximoyt chloride (1.2 g. 4.4 mmol) described in Manufacturing Example 1-1.3 and tetrahydrofurus (3.4 ml.) were added 3-Ethynyl-pydrine-2ylamine (2.60 mg, 2.2 mmol) described in Manufacturing Example 1-2.9 and triethylamine (3.0 ml., 22 mmol) at 0°C, which was stirred for 1 hour at room temperature. To the reaction mixture was added water at room temperature, which was then extracted with ethyl acetate-tetrahydrofurun (2.1). The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1.3) to obtain the title compound (24.0 mg, 15%).

1H-NMR Spectrum (CDCb₂) δ (ppm); 4.00 (2H, s), 5.05 (2H, s), 5.41 (2H, s), 6.24 (1 H, s), 6.71 (1 H, dd, J = 4.9, 7.6 Hz), 6.33-6.97 (2H, m), 7.18-7.22 (2H, m), 7.31-7.44 (5H, m), 7.70 (1 H, dd, J = 1.7, 7.6 Hz), 6.13 (1 H, dd, J = 1.8, 4.9 Hz). The starting material, 4-benzyloxy-phenyl-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 1-1-1] 1 -Benzyloxy-4-((E)-2-nitro-vinyl)-benzene

[0340]

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[0341] To a mixture of 4-benzyloxybenzaldehyde (1.0 g, 4.7 mmol) and sodium methoxide (28% methanol solution, 150 µ, 0.74 mmol) and methanol (10 ml.) were added nitromethane (330 µ, 6.1 mmol) and sodium methoxide (28% methanol solution, 1.0 ml., 4 a mmol) at 0°C, which was stirred for 10 minutes at room temperature. The reaction mixture was cooled to 0°C, and 5 N aqueous hydrochloric acid solution (20 ml.) was added thereto at the same temperature. The reaction mixture was then stirred for 15 minutes at room temperature. The precipitated solids were filtered to obtain the title compound (1.2 g, 109%).

¹H-NMR Spectrum (DMSO-d₀) δ (ppm): 5.20 (2H, s), 7.10-7.14 (2H, m), 7.32-7.48 (5H, m), 7.82-7.85 (2H, m), 8.12 (2H, dd. J = 13.5, 18.2 Hz).

[Manufacturing Example 1-1-2] 1-Benzyloxy-4-(2-nitro-ethyl)-benzene

[0342]

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[0343] To a mixture of 1-benzyloxy-4-((E)-2-nitro-vinyl)-benzene (1.0 g, 3.9 mmol) described in Manufacturing Example 1-1-1, acetic acid (1 mL) and dimethyl sulfoxide (17 mL) was added sodium borohydride (260 mg, 6.3 mmol) at room temperature within cooling appropriately, and the reaction mixture was stirred for 40 minutes at room temperature. Water was added to the reaction mixture. The reaction mixture was partitioned into ethyl acetate and water. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium suifate, and the solvent was exponted under a reduced pressure. The residue was purified by MH siding electioner chomolography

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(ethyl acetate: heptane = 1:3) to obtain the fitle compound (710 mg, 70%).

14-NMR Spectrum (CDCl₀) & (pgm): 2-86 (2H, t, J = 7.2 Hz), 4.56 (2H, t, J = 7.2 Hz), 5.04 (2H, s), 6.92 (2H, d, J = 8.4 Hz), 7.11 (2H, d.) = 8.8 Hz, 7.30 7.42 (5H, m).

5 [Manufacturing Example 1-1-3] 4-Benzyloxy-phenyl-acetohydroximoyl chloride

[0344]

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[0345] To a mixture of 1-benzyloxy-4-(2-nitro-ethyl)-benzene (340 mg, 1.3 mmol) described in Manufacturing Example 1-1-2 and methanol (5 mL) was added lithium methoxide (100 mg, 2.6 mmol) at room temperature, which was stirred for 15 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. Methylene chioride (4 mL) and tetrahydrofuran (2 mL) were added to the residue. Titianium (IV) chioride was added at -78° C to the reaction mixture, which was then sittred for 50 minutes at 0°C. The reaction mixture was cooled to -78° C, and after adding water (5 mL), the reaction mixture was partitioned into ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chioride, and the solvent was evaporated under a reduced pressure. The residue was purified by neutral silica gel column chromatography (ethyl acetate: heptane = 1: 3) to obtain the title compound (310 mg, 84%).

[Manufacturing Example 1-2-1] 3-lodopyridin-2-ylamine

The starting material, 3-ethynyl-pyridin-2-ylamine, was synthesized as follows.

[0346]

NH.

[0347] A mixture of IN-(3-lodopyridin-2-yl-2-d'imethyl-projionamide (68.2 g. 216 mmol) described in Manufacturing Example 39-1-2, 5 N aqueous sodium hydroxide solution (200 mL) and methanol (200 mL) was stirred under reflux for 1 hour and 20 minutes. The reaction solution was allowed to room temperature and partitioned into water and ethyl acetate. The aqueous layer was extracted with ethyl acetate three times. The organic layers were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration, and the solvent was concentrated under a reduced pressure to obtain the title compound (41.2 g, 65.9%). 11-HMR Spectrum (DMSO-d₀) δ (ppm): 6.00 (2H, brs), 6.32 (1H, dd, J = 4.8 Hz, 7.2 Hz), 7.87 (1H, d, J = 7.2 Hz), 7.92 (1H, d, J = 7.8 Hz), 7.92 (1H, d, J = 7.8 Hz), 7.93 (1H, d, J = 7.8 Hz), 7.94 (1H, d, J = 7.8 Hz), 7.95 (1H, d, J = 7.8 Hz

[Manufacturing Example 1-2-2] 3-Trimethylsilanylethynyl-pyridin-2-ylamine

[0348]

[0349] To a mixture of 3-iodopyridin-2-ylamine (40.2 g, 183 mmol) described in Manufacturing Example 1-2-1, trimethysisiyacetylene (E.7 mL, 366 mmol), copper (I) iodide (3.4 g, 18.3 mmol), M.N-diisopropylethylamine (63.7 mL, 366 mmol) and N-methylgyroldinone (200 mL) was added tetrakski(tripharylphosphine)palladum (I) 0.6 g, 9.15 mmol) under ritrogen atmosphere, which was stirred for 3 hours and 10 minutes at room temperature. Water was added to the reaction solution, which was three attracted with eithyl acetate 4 mess. The evolvent was concentrated under a reduced pressure. The residue was purified by NH silica gel chromatography (heptane: ethyl acetate 4-1). The resulting solution was concentrated under a reduced pressure, and the residue was purified by silica gel chromatography (heptane: ethyl acetate 2: 1 then 1: 1) to Obtain the title compound (28.1 g, 80.7%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.25 (9H, s), 6.09 (2H, brs), 6.51-6.57 (1 H, m), 7.50-7.55 (1 H, m), 7.95-7.99 (1 H, m).

[Manufacturing Example 1-2-3] 3-Ethynyl-pyridin-2-ylamine

[0350]

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[0551] To a solution of 3-trimethylalisnylethynyl-pyridine-2ylamine (28.1 g, 148 mmol.) described in Manufacturing Example 1-2-2 in tetrahydrofuran (300 ml.) was added tetrabulylammonium fluoride (1 M tetrahydrofuran solution, 20 ml., 20 mmol), which was stirred for 15 minutes at room temperature. Water was added to the reaction solution, which was then extracted with ethyl acetate 4 times. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel chromatography (heptane: ethyl acetate 4 : 1: then 1: 2) to obtain the title compound (16.4 g, 93.7%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 4.43 (1 H, s), 6.14 (2H, brs), 6.53 (1 H, dd, J = 4.8 Hz, 7.2 Hz), 7.53 (1 H, d, J = 7.2 Hz), 7.96 (1 H, d, J = 4.8 Hz).

[Manufacturing Example 1-3-1] 3-Trimethylsilanylethynyl-pyridin-2-ylamine (Alternative Method)

5 [0352]

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[0353] To a solution of 2-amino-3-bromopyridine (5.72 g, 33.1 mmol) in N-methylpyrrolidinone (120 mL) were added

trimethysishy acetylene (8,28 mL, 68.2 mmol), tetrakis(triphenylphosphine)palladum (0) (1,91 g. 1,66 mmol), ocoper (1) iodide (830 mg, 3.31 mmol) and NJA-disorpylethylamine (11,5 mL, 66.2 mmol) at room temperature, which was stirred under nitrogen atmosphere for 6 hours at 70°C. Where was added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over enhydrous reapesium suitlate, and the solvent was everporated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl acetate = 2.1) to obtain the title compound (5,94 g., 94%).

11-HAMR Spectrum (DMSO-dg) 6 (ppmi): 0.23 (9H, s), 6.07 (2H, brs), 6.51 (1 H, dd, J = 4,9, 7.5 Hz), 7.49 (1 H, dd, J = 1,8, 7.5 Hz), 7.49 (1 H, dd, J = 1,4,9 Hz).

© [Example 2] 3-(3-(4-(Pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0354]

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[0355] To a solution of (4-(pyridin-2-yloxymethyl)-phenyl)-eactohydroximoyl chloride (510 mg. 1.84 mmol) described in Manufacturing Example 2-1-5 and 3-ethynylpyridin-2-ylamine (150 mg. 1.27 mmol) described in Manufacturing Example 1-2-3 in letrahydrofuran (5 ml.) was added triethylamine (706 gl., 5.08 mmol) at room temperature, which was stirred for 95 minutes at room temperature. Water was added at room temperature to the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous oddium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane : ethyl acetate = 2 : 1) to obtain the title compound (120 mg. 26%). H-NMR Spectrum (COCL) § (pomyl. 40.6) (E14, 5.37 (E14, 6.3.63 (E14, 6.5, 6.45 (E14, 6.5, 6.76 4.62 (E14, 6.5, 6.65 (E14, 6.5, 6.76 4.62 (E14, 6.5, 6.65 (E14, 6.5), 6.76 4.62 (E14, 6.5), 6.76 (E14, 6.5),

(1 H, m), 7.30 (2H, d, J = 8.1 Hz), 7.45 (2H, d, J = 8.1 Hz), 7.57-7.61 (1 H, m), 7.85 (1 H, d, J = 7.3 Hz), 8.03 (1 H, d, J = 8.5 Hz), 7.57-7.61 (1 H, m), 7.85 (1 H, d, J = 7.3 Hz), 8.03 (1 H, d, J = 5.5 Hz), 8.17 (1H, m).

The starting material; (4-(pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 2-1-1] (4-(Pyridin-2-yloxymethyl)-phenyl)methanol

[0356]

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46 [0357] To a mixture of 1,4-benzenedimethanol (5.5 g, 40 mmol), 2-fluoropyridine (1.3 g, 13 mmol) and N,N-dimethyl-formamide (15 ml.) was added sodium hydride (1.4 g, 40 mmol, 68% in 0) ita 0°C, which was stirred for 20 minutes at room temperature and for 1 hour at 70°C. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1: 1) to obtain the title compound (1.9 g, 66%).

 1 H-NMR Spectrum (CDCl₃) 3 (ppm): 4.71 (2H, s), 5.38 (2H, s), 6.81 (1 H, td, J = 0.9, 8.4 Hz), 6.89 (1 H, ddd, J = 0.9, 5.1, 7.1 Hz), 7.37-7.47 (4H, m), 7.59 (1 H, ddd, J = 2.0, 7.1, 8.3 Hz), 8.17 (1 H, ddd, J = 0.7, 2.0, 5.1 Hz).

[Manufacturing Example 2-1-2] 4-(Pyridin-2-yloxymethyl)-benzaldehyde

[0358]

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[0359] To a mixture of (4-(pyridin-2-yloxymethyl)-phenylymethanol (1.9 g, 8.6 mmol) described in Manufacturing Example 2-1-1 and methylene chloride (30 m.l.) was added manganese dioxide (15 g, 17 mmol) at room temperature, which was stirred overnight at that temperature. The reaction mixture was filtered through a Cellite pad, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : heptane = 1 - 41 to betain the title compound f70 mo. 42%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 5.48 (2H, s), 6.85 (1 H, d, J = 8.2 Hz), 6.90-6.93 (1 H, m), 7.60-7.64 (3H, m), 7.89 (2H, d, J = 8.1 Hz), 8.16 (1 H, dd, J = 1.3, 4.9 Hz), 10.0 (1 H, s).

[Manufacturing Example 2-1-3] 2-(4-((E)-2-Nitro-vinyl)-benzyloxy)-pyridine

[0360]

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[0361] A mixture of 4-(pvidin-2-yloxymethyl)-benzaldehyde (23.4 g, 110 mmol) described in Manufacturing Example 2-12, Intromethen (38.8 g, 560 mmol), ammonlum ecestes (17.0 g, 220 mmol) and acete bed (200 ml.) was stirred for 1 hour and 45 minutes at 100°C. The reaction solution was etimed on an loe bath while adding a small amount of water, and the preciolitated solide were filtered to obtain the title commount @1.0 q. 7.45 ml.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 5.41 (2H, s), 6.91 (1 H, dd, J = 0.8, 8.4 Hz), 6.99-7.10 (1 H, m), 7.53 (2H, d, J = 8.0 Hz), 7.72-7.79 (1 H, m), 7.86 (2H, d, J = 8.0 Hz), 8.15-8.20 (1 H, m), 8.23 (1 H, d, J = 10 Hz).

[Manufacturing Example 2-1-4] 2-(4-(2-Nitro-ethyl)-benzyloxy)-pyridine

[0362]

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[0363] To a solution of 2-(4-((E)2-nitro-vinyl-benzyloxy)-pyridine (21.0 g. 81.9 mmol) described in Marufacturing Example 2-1.5, sectic acid (21 mL) in dimethy sulforide (200 mL) was edded sodium borohydride (4.98 g. 31.5 mmol) at room temperature while cooling appropriately. After addition of sodium borohydride, the cooling bath was removed, followed by stirring for 15 minutes at room temperature. The reaction solution was partitioned into waster and ethyl accetate. The ethyl accetate slayer was weather with water twice and with saturated aqueues sodium chlorida one, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by Mr slicing electionm chromatography (ethyl accetate; helpane = 1: 3) to obtain the title compound (16.3 g. 77.1 %). H-NMR Spectrum (DMSO-d₂) 6 (ppm): 323 (2H, 1, 9 = 6.8 Hz), 4.85 (2H, 1, 1 = 6.8 Hz), 5.82(2H, 5, 8.22,6.88 (1 H, m), 6.98-7.01 (1 H, m), 7.28 (2H, 4, 1) = 8.0 Hz), 7.89-7.74 (1 H, m), 8.15-8.19 (1 H, m).

[Manufacturing Example 2-1-5] 4-(Pyridin-2-yloxymethyl)-phenyl-acetohydroximoyl chloride

[0364]

[0365] Lithium wire (825 mg, 46.6 mmol) was added to and dissolved in methanol (75 mL). To the mixture solution was added 2-(4-2-nitro-thy-benzyoxy)-pyringine (6.0 g, 23.3 mmol) described in Mauritadrumg Exemple 2-1-4. The reaction solution was concentrated under a reduced pressure. Tolurine was added to the recidue, and the solvent was concentrated under a reduced pressure. A solution of the resulting residue in methylere chloride (90 mL) and tetrahy-drufuran (45 mL) was cooled to - 78°C, and fitanium (IV) chloride, (8.15 mL, 74.4 mmol) was added write stirring was added virile stirring and the solution was pround into an ice water and extracted with eithyl acettact. The organic layer was dried over anhydrous magnesium sulfate, and the magnesium sulfate was removed by filtration. The filtrate was passed through a glass filter covered with neutral siting and was added to the residue, and the pre-clothated solids were filtered and out to obtain the title compound (1.6 s. 2.8 x%).

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.82 (2H, s), 5.33 (2H, s), 6.84-6.89 (1 H, m), 6.97-7.01 (1 H, m), 7.25 (2H, d, J = 8.4 Hz), 7.41 (2H, d, J = 8.4 Hz), 7.70-7.76 (1 H, m), 8.15-8.18 (1 H, m), 11.7 (1H, s).

[Example 3] 3-(3-(4-(6-Methyl-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

25 [0366]

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40 [0367] To a solution of 3-ethynyl-pyridin-2-ylamine (30 mg, 0.25 mmol) described in Manufacturing Example 1-2-3 in anlydrous tetrahydroturan (6 mL) was added (4-(6-methyl-pyridin-2-yloxymethyl)-phenyl-acetohydroximoyl chloride (222 mg, 0.76 mmol) described in Manufacturing Example 3-1-5 under nitrogen atmosphere at room temperature. Triethyamine (142 µL, 1.0 mmol) was added dropvise to the reaction solution, and stirred overnight at room temperature. The reaction mixture was peritioned nitro vater and ethyl acetate. The organic leyer was vashed with water and saturated acueuous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was eveporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1: 3 then 1: 1) to obtain the title compound (10.5 mg, 11 %).

114-1MM Spectrum (DMSO-d₄) 8 (ppm): 2.39 (3H, s), 4.04 (2H, s), 5.29 (2H, s), 6.26 (2H, brs), 6.61-6.64 (1 H, m), 6.68-6.71 (1 H, m), 6.81 (1 H, s), 6.83 (1 H, d, J = 7.2 Hz), 7.33 (2H, d, J = 8.0 Hz), 7.42 (2H, d, J = 8.0 Hz), 7.57-7.61 (1 H, dd, J = 7.2, 8.4 Hz), 7.87 (1 H, dd, J = 2.0, 7.6 Hz), 8.08 (1 H, dd, J = 7.2, 8.4 Hz), 7.87 (1 H, dd, J = 2.0, 7.6 Hz), 8.08 (1 H, dd, J = 7.2 Hz, 6.0 Hz).

The starting material, (4-(6-methyl-pyridin-2-yloxymethyl)-benzene)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 3-1-1] 2-(4-Bromo-benzyloxy)-6-methyl-pyridine

[0368]

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[0389] To a solution of (4-bromo-phenyl)-methanol (4.54 g. 2.4.3 mmol) in N.N-dimethylformamide (50 mL) was added sodium hydride (999 mg, 25 mmol, 60% in oil) under nitrogen atmosphere on an ice bath (0°C), which was stirred for 30 minutes at room temperature. 2-Fluoro-6-methylpyridrine (1.8 g. 16.2 mmol) was then added to the reaction mixture on an ice bath (0°C), and stirred for 5 hours at room temperature. The reaction mixture was partitioned into water and eithy acetate on the ice bath (0°C). The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : heptane = 1 : 15) to obtain the title compound (3.65 g, 81%).

3,5-0-7,1 1H-NMR Spectrum (CDCl₃) δ (ppm): 2.44 (3H, s), 5.32 (2H, s), 6.57-6.59 (1 H, m), 6.71-6.74 (1H, m), 7.26-7.35 (2H, m), 7.44-7.49 (3H m).

[Manufacturing Example 3-1-2] 4-(6-Methyl-pyridin-2-yloxymethyl)-benzaldehyde

[0370]

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[0371] Under nitrogen atmosphere, to a solution of 2-(4-bromo-benzyloxy)-6-methyloyridine (7.30 g, 26.2 mmol) described in Manufacturing Example 3-1-1 in anthyrotus tetrahyridomtun (200 mt.) was added droywise n-brolly lithium (2.67 M n-hexane solution, 11.8 mt., 31.4 mmol) on a dry loe-ethanol bath (-78°C), which was stirred for 30 minutes at -78°C. Ni-dimethylformamide (4.04 mt., 52.4 mmol) was added to this mixture at -78°C, and sirred for 5 minutes. Water and ethyl sectled were added to the reaction mixture, which was sirred for 10 minutes at room temperature, and the organic layer was then separated. This organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesiam usuffate, and the solvent was exponented under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 1 : 3) to obtain the title compound (4.19 o. 70%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.44 (3H, s), 5.46 (2H, s), 6.12-6.64 (1H, m), 6.74-6.75 (1 H, m), 7.44-7.50 (1 H, m), 7.62 (2H, d, J = 8.0 Hz), 7.88 (2H, d, J = 8.0 Hz), 10.0 (1 H, s).

[Manufacturing Example 3-1-3] 2-Methyl-6-(4-((E)-2-nitro-vinyl)-benzyloxy)-pyridine

[0372]

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[0373] To a solution of 4-(6-methyl-pyridin-2-yloxymethyl)-benzaldehyde (4.19 g, 18.5 mmol) described in Manufacturing Example 3-1-2 in acetic acid (30 mL) were added nitromethane (5.65 g, 92.6 mmol) and ammonium acetate (2.85

g, 37.0 mmol) under nitrogen atmosphere, which was stirred for 3 hours at 110°C. The reaction mixture was partitioned into water and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and orlied over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure to obtain the title compound (5,50 o) as a crude product.

⁵ ¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.45 (3H, s), 5.43 (2H, s), 6.05-6.28 (1 H, m), 6.74-6.76 (1H, m), 7.47-7.51 (1 H, m), 7.55 (4H, s), 7.59 (1 H, d, J = 13.6 Hz), 8.01 (1H, d, J = 13.6 Hz).

[Manufacturing Example 3-1-4] 2-Methyl-6-(4-(2-nitro-ethyl)-benzyloxy)pyridine

[0374]

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[0375] To a solution of 2-methyl-6-(4-((B)-2-nitro-vinyl)-benzyloxy)-pyrkline (S.0.0 g., 18.5 mmol) described in Mamuraturing Example 3-13 and acets cald (5 m.l.) in intently sulforder (50 m.l.) was acided a oddium bronivylaride (1.2 g., 29.6 mmol) under nitrogen atmosphere at room temperature while cooling appropriately, which was stirred for 10 minutes at room temperature. Water was then added dropwise. The mixture was partitioned into water and ethyl acetale. The organic layer was weshed with water and saturated aqueous sodium orbiforiae, and dred over annydrous regnesium sulface, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (chity acetate: heptane = 1: 5 then 1: 2) to obtain the title compound (2.9, 56%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.39 (3H, s), 3.22 (2H, t, J = 6.8 Hz), 4.85 (2H, t, J = 6.8 Hz), 5.28 (2H, s), 6.64 (1 H, d, J = 8.0 Hz), 7.84 (1 H, d, J = 8.0 Hz), 7.28 (2H, d, J = 7.6 Hz), 7.39 (2H, d, J = 7.6 Hz), 7.59 (1 H, t, J = 8.0 Hz).

[Manufacturing Example 3-1-5] (4-(6-Methyl-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride

[0376]

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[0377] To a solution of 2-methyl-6-(4-(2-nitro-ethyl)-benzyloxy)pyridine (500 mg, 1.84 mmol) described in Manufacturing Example 31-4 in methanol (10 mL) was added lithum methoxide (140 mg, 3.08 mmol) under nitrogen entempehere at room temperature, which was stirred for 30 milhules at room temperature. The reaction mixture was concentrated under a reduced pressure. Anhydrous methylene chloride (10 mL) and anhydrous tetrahydrouran (5 mL) were added to the residue. Titalnium (10) chlorid (667 µL, 607 mmol) was added dropwise to the reaction mixture on a divice thanol bath (78°C), and stirred for 45 minutes at 0°C. The reaction mixture was then stirred for further 60 minutes at room temperature. Water, ethyl acetate and tetrahydrofuran were added to the reaction mixture on an lot bath (0°C), and the organic layer was separated. This organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure to obtain the title compound (464 mg, 91 %) as a crude product.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.42 (3H, s), 3.82 (2H, s), 5.33 (2H, s), 6.76 (1H, d, J = 7.6 Hz), 6.92 (1 H, d, J = 7.6 Hz), 7.27 (2H, d, J = 8.0 Hz), 7.44 (2H, d, J = 8.0 Hz), 7.70 (1 H, t, J = 7.6 Hz), 11.8 (1 H, brs).

[Example 4] 3-(3-(4-Butoxymethyl-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0378]

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19 (0379) To a solution of 4-butcoymethy-phenyl-acetohydroximoyi chloride (28 mg, 0.11 mmol) described in Manufacturing Example 4-14 and 3-ethymyl-pyridin-2-ylamine (13 mg, 0.11 mmol) described in Manufacturing Example 1-23 in tetrahydroturan (1 mt) was added triethylamine (31 µL, 0.22 mmol) at room temperature, which was stirred for 70 minutes at room temperature. The reaction solution was partitioned into water and ethyl acetate at room temperature. The organic layer was washed with saturated aqueous sodium chridred and dried over anhydrous magnesiem sulfate.
28 and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane : ethyl acetate = 2 : 1) and then further purified by reverse-phase high performance liquid chromatography (using an acetontrifie-water mobile) phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (2.3 mg, 5%) as a trifluoroacetic acid sat.
MS me (55) (MH) 338.1 (MH)

5 The starting material, 4-butoxymethyl-phenyl-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 4-1-1] 1-Bromo-4-butoxymethyl-benzene

[0380]

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[0381] To a solution of 4-bromobenzyl alcohol (10.0 g, 53.5 mmol) in N,N-dimethylformamide (200 mL) was added sodium hydride (5.0 g, 6.4 mmol, 50% in oil) at 0°C. This mixture was stirred for 5 minutes at 0°C, and 1-bromobutane (7.4 mL, 9.5 mmol) was added therefor at 0°C. This mixture was stirred for 40 minutes at 0°C method at 0°C. The organic layer was washed with water and started of 0°C. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnedium sulfate, and the solvent was evaporated under a reduced pressure. The residue was puffied by slica gel column chromatography (heptane : ethy scateate = 20 : 1) to obtain the title compound (11.5 g, 98%).

¹H-NMR Spectrum (CDCl₂) δ (ppm): 0.919 (3H, t, J = 7.3 Hz), 1.35-1.44 (2H, m), 1.56-1.63 (2H, m), 3.46 (2H, t, J = 6.6 Hz), 4.45 (2H, s), 7.21 (2H, d, J = 8.1 Hz), 7.45-7.48 (2H, m).

[Manufacturing Example 4-1-2] 4-Butoxymethyl-benzaldehyde

50 [0382]

10 [0383] To a solution of 1-bromo-4-butosymethyl-benzene (11.5 g, 47.3 mmol) described in Manufacturing Example 4:1-1 in tetrahydrofuran (200 mL) was added n-butyl tithium (32.5 mL, 1.6 M hexane solution, 52.0 mmol) at -78°C. This mixture was stirred for 55 minutes at 78°C, and N,N-dimethylformamide (4.4 mL, 56.8 mmol) was added thereto at -78°C. This mixture was warmed to room temperature, and stirred for 20 minutes. The reaction solution was partitioned into water and ethyl accetate at 0°C. The originate layer was washed with saturated aqueous sodium choride and dried of the solution of the so

Manufacturing Example 4-1-3] 1-Butoxymethyl-4-(2-nitroethyl)-benzene

[0384]

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[0385] To a solution of 4-butoxymethyl-benzaldehyde (7.39 g, 3.84 rmnol) described in Manufacturing Example 4.1-2 in methanol (14 Mm) was added intromethane (2.70 ml., 4.99 mm) followed by sodium methoxide (1.494 methanol solution, 9.41 ml., 4.61, mmol) at 0°C. The reaction solution was stirred for 30 minutes at room temperature, and 5 N aqueous hydrochrior acid solution (120 ml.) was added there to an dirred for further 25 minutes. This reaction solution was partitioned into saturated aqueous sodium chloride and ethyl scetate at 0°C. The organic layer was washed with saturated aqueous dedulm chloride and eried over anity routous magnesium sulfate, and the solvent was evaporated under a reduced pressure. To a solution of the resulting residue in dimethy sulfoxide (10 ml.) and sectle acid (6 ml.) was added sodium borohydride (1.84 g, 46.1 mmol) at room temperature while cooling appropriately. This solution was then stirred for 80 minutes at room temperature. The reaction solution was partitioned into water and erityl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by sitiac gel column chromatography (haptane: ethyl sectlate = 4 : 1) to obtain the title compound (2.88 g, .29%).

Hz), 3.47 (2H, t, J = 6.6 hz), 4.47 (2H, s), 4.60 (2H, t, J = 7.3 Hz), 7.18 (2H, d, J = 8.2 Hz), 7.30 (2H, d, J = 8.2 Hz).

[Manufacturing Example 4-1-4] 4-Butoxymethyl-phenyl-acetohydroximoyl chloride

0 [0386]

[0387] To a solution of 1-butosymethyl-4-(2-nitoethyl-berzene (55 mg, 0.23 mmol) described in Manufacturing Example 4-1-3 in methanol (2 ml.) was added sodium methoxide (1.49 M methanol solution, 47.3 µL.) 0.23 mmol) at 0°C. The reaction solution was stirred for 35 minutes at room temperature, and concentrated under a reduced pressure. To a solution of the residue in methylene chloride (2 ml.) was added titanium (IV) chloride (28 µL.) 0.23 mmol) under nitrogen atmosphere at -76°C, which was then stirred for 30 minutes at 0°C. The reaction solution was partitioned into water and ethyl acetate at 0°C. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the magnesium sulfate was removed by filtration. The organic layer was filtered with size gel, and the filtrate was evaporated under a reduced pressure to obtain the title compound (59 mg, 99%) as a crude product. 11-h-NMR Spectrum (CDCL) 5 (ppm): 0.90-0.94 (3H, m), 1.36-1.44 (2H, m), 1.56-1.64 (2H, m), 3.46-3.49 (2H, m), 3.79 (2H, a), 4.50 (2H, a), 7.29-7.26 (4F, m), 7.39-7.34 (2H, m), 8.29 (1H, m), 8.29 (1H, m), 8.29 (1H, m), 8.46-3.49 (2H, m), 3.46-3.49 (2H, m), 3.79 (2H, m), 8.29 (2H, m), 8.29 (1H, m),

[Example 5] 3-(3-(4-(2-Fluoro-benzyloxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0388]

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[0389] To a mixture of 4-5f-(2-mino-pyridin-3-y)(soxazo1-3-y)(methyl-phenol (4.2 mg, 0.016 mmol) described in Manutacturing Example 5-1-1 and methanol (0.4 mL), was added 1 N aqueous sodium hydroxide solution (16 µL, 0.015 mmol). This mixture was concentrated under a reduced pressure. To a mixture of the residue and N-N-dimethylformarride (0.5 mL) was added 2-thorocherxyl bromide (2.3 µL, 0.019 mmol), which was stirred for 1 hour at room temperature. The reaction mixture was then purified directly by reverse-phase high performance (iguid chromotography (using an acetonitrile-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (3.3 mg, 43%) as a frifluoroacetic acid salt.

MS m/e (ESI) 376.14 (MH+)

The starting material, 4-(5-(2-amino-pyridin-3-yl)isoxazol-3-ylmethyl)-phenol, was synthesized as follows.

[Manufacturing Example 5-1-1] 4-(5-(2-Amino-pyridin-3-yl)isoxazol-3-ylmethyl)-phenol

8.6 Hz), 7.87 (1 H, dd, J = 1.5, 7.7 Hz), 8.10 (1 H, brs), 9.29 (1H, s).

[0390]

[0391] To a mixture of 3-(3-(4-benzylosy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine (32 mg. 0.090 mmol) described in Example 1 and trifluoroscotic acid (1 ml.) was added thiosnisole (45 mg. 0.38 mmol) at room temperature, which was stirred for 2 hours at the same temperature. To a mixture of saturated aqueous sodium hydrogencarbonate solution and ethyl acetate was added the reaction mixture. The organic layer was separated and wested with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: heptane = 4: 1) to obtain the title compound (24 mg. 100%).

[Example 6] 3-(3-(4-(3-Fluoro-benzyloxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0392]

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[0393] To a mixture of 4-(f-(2-amino-pyridin-3-yy)(soxzac)4-y/methyl)-phenol (4.2 mg, 0.016 mmol)described in Mandacturing Exemple 5-1-1 and methanol (0.4 mt), was added 1 N aquesus sodium hyproided solution (if a jul, 0.016 mmol), which was then concentrated under a reduced pressure. To a mixture of the residue and N,N-dimethylformenide (0.5 mt), was added 3-fluorobenzy bromides (2.3 µL, 0.019 mmol), which was stirred for 1 hour at room temperature. The reaction mixture was purified directly by reverse-phease high performance liquid chromatography (using an acetonitrie-water mobile phase containing 0.1% trifluoroacetic acid) to obtain the title compound (4.3 mg, 55%) as a trifluoroacetic acid salt.

MS m/e (ESI) 376.12 (MH+)

[Example 7] 3-(3-(4-(4-Fluoro-benzyloxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0394] To a mixture of 4-(6-(2-amino-pyridin-2-yi)[soxzac1-3-yinethyly-phenol (2.2 mg, 0.016 mmol) described in Manriccturing Example 5-1-1 and methanol (0.4 mt.) was added 1 N aqueous sodium hydroxide solution (16 µt, 0.016 mmol), which was then concentrated under a reduced pressure. To a mixture of the residue and N.N-dimetryl/ormamide (0.5 mt.), was added 4-fluorobaryl bromide (2.3 µt, 0.019 mmol), which was stirred for 1 hour at room temperature. The reaction mixture was purified as is by reverse-phese high performance liquid chromatography (using an acostonitilewater mobile phese containing 0.1% trifluoroacetic acid) to obtain the title compound (3.1 mg, 39%) as a trifluoroacetic acid salt.

MS m/e (ESI) 376.12 (MH+)

[Example 8] 3-(3-(4-Cyclopropylmethoxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0395]

[0396] To a mixture of 4-(5-(2-amino-pyridin-3-y))[soxzaol-3-y/methyly-phenol (2,2 mg, 0.016 mmol) described in Maniducturing Example 5-1-1 and methanol (0.4 ml), was added 1 N aqueous sodium hydroxide solution (16 µJ, 0.016 mmol), which was then concentrated under a reduced pressure. To a mixture of the residue and N, N-dimethylformamide (0.5 ml), were added cyclopropylmethyl bromide (2.3 µL, 0.019 mmol) and sodium iodde (1 mg, 7 µmol) at room temperature, which was stirred for 2 hours at 80°C. The reaction mixture was cooled to room temperature and then purified as is by reverse-phase high performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % "influoreacetic acid). The elutate was neutralized by trithyramine while being concentrated. The solvent was evaporated under a reduced pressure. The residue was washed with water to obtain the title compound (1.6 mg, 30%). MS m/e (ESI) 322 19 (MH¹)

[Example 9] 3-(3-(4-(Pyridin-2-vlmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-vlamine

[0397]

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28 [039] To a mixture of 4-(6-(2-amino-pyridin-3-y))sovazo-8-yimethyly-phenol (4.2 mg, 0.016 mmol) described in Manufacturing Example 5-1-1 and methanol (0.4 mL) was added 1 N aqueous sodium hydroxide solution (16 µL, 0.016 mmol), which was then concentrated under a reduced pressure. To a mixture of the residue and NN-dimethyfromamide (0.5 mL) was added 2-picolyl chloride (3.1 mg, 0.019 mmol), which was stirred for 2 hours at room temperature. The reaction mixture was purified as is by reverse-phase high performance liquid chromatography (using an acciontridewater mobile phase containing 0.1 % trifluroraceitic acidy) to obtain the title compound (3.6 mg, 3.9%) as diffurioraceitic.

acid salt. MS m/e (ESI) 359.16 (MH+)

[Example 10] 3-(3-(4-(6-Methyl-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0399]

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[0400] Methano (g m.l.) and 1 N aqueous sodium hydroxide solution (0.18 m.l.) were added to 4/6-f/2-amino-pyridin-3-yl)soxazol-3-ylmethyl)-phenol (50 mg, 0.19 mmol) described in Manufacturing Example 5-1-1, which was then dissolved by irradfating ultrasonic wave. This solution was concentrated under a reduced pressure. To the resulting residue were added 2-chioromethyl-6-methyl-byridine (31.8 mg, 0.22 mmol) described in Manufacturing Example 10-1-1 and NN-dimethylomarnide (2 m.l.), which was stired for 20 minutes at 60°C. The reaction solution was partitioned into water and ethyl acetate. The organic layer was separated, and the solvent was evaporated under a reduced pressure. The residue was purified by NH sitica gel column chromatography (heptane: ethyl acetate = 1: 1) to obtain the title compound (38 mg, 51.7%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.48 (3H, s), 3.96 (2H, s), 5.10 (2H, s), 6.25 (2H, brs), 6.69 (1 H, dd, J = 4.8, 8.0 Hz), 6.79 (1H, s), 6.97 (2H, d, J = 8.0 Hz), 7.14 (H, d, J = 7.6 Hz), 7.25 (2H, d, J = 8.0 Hz), 7.27 (1 H, d, J = 7.6 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.27 (1 H, d, J = 7.6 Hz), 7.27 (1 H, dd, J = 7.6 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.27 (1 H, d, J = 7.6 Hz), 7.27 (1 H, dd, J = 7.6 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.27 (1 H, d, J = 8.0 Hz), 7.27 (1 H, d, J = 7.6 Hz), 7.27 (1 H, d, J =

The starting material, 2-chloromethyl-6-methyl-pyridine, was obtained as follows.

[Manufacturing Example 10-1-1] 2-Chloromethyl-6-methyl-pyridine

[0401]

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CI

[0402] A solution of (6-methyl-pyridin-2yl)-methanol (1.44 g. 1.17 mmol), thionyl chloride (1.45 ml., 1.9.9 mmol) and methylene chloride (20 ml.) was stirred under reflux for 40 minutes. The reaction solution was cooled to room temperature and then concentrated under a reduced pressure. The residue was partitioned into sodium bicarbonate solution and delatifyl either. The organic layer was concentrated under a reduced pressure, and the residue was purified by silica gel chromatocraphy (ethyl scateta) to obtain the title compound (1.42 g. 8,58%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.47 (3H, s), 4.72 (2H, s), 7.22 (1H, d, J = 7.6 Hz), 7.33 (1 H, d, J = 7.6 Hz), 7.72 (1 H, dd, J = 7.6, 7.6 Hz).

20 [Example 11] 3-(3-(4-(4-Methyl-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0403]

NH,

48 (Q404] Methanol (3 mL) and 1 N aquaous sodium hydroxide solution (0.18 mL) were added to 4/5-(2-amino-pyridine-3-yillossoza/e-3-yillenstyn-3-benol (50 mg. 0.19 mno) described in Manufacturing Example 5-1-1, which was then dissolved by irradiating ultrasonic wave. This solution was concentrated under a reduced pressure. To the resulting residue were added 2-chloromethyl-4-methyl-pyridine (3.1.8 mg, 0.22 mmol) described in Manufacturing Example 11-1-4 and NI-dimethylformamide (2 mL), which was sifted for 10 minutes at 60°C. The reaction solution was partitioned into 90 water and ethyl acetate. The organic layer was separated, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: e1thyl acetate 1 : 1) to obtain the title.

compound (21 mg, 30.2%).

1H-NMR Spectrum (DMSO-d₀) δ (ppm): 2.33 (3H, s), 3.96 (2H, s), 5.11 (2H, s), 6.25 (2H, brs), 6.69 (1 H, dd, J = 4.8, 8.0 Hz), 6.79 (1 H, s), 6.98 (2H, d, J = 8.4 Hz), 7.17 (1 H, d, J = 7.6 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.34 (1 H, s), 7.87 (1 H, d, J = 7.8 Hz), 8.09 (1 H, d, J = 8.4 Hz), 8.41 (1 H, d, J = 4.8 Hz).

The starting material, 2-chloromethyl-4-methyl-pyridine, was synthesized as follows.

[Manufacturing Example 11-1-1] 2,4-Dimethyl-pyridine 1-oxide

50 [0405]

[0406] To a solution of 2.4 - futidine (2.0 g. 18.7 mmol) in methylene chloride (100 mL) was added 3-chloroperoxybenzoic acid (5.07 g. 29.4 mmol), which was sitted of 20 minutus at room temperature. A small amount of saturated aqueous sodium hydrogen sulfite solution was added to the reaction solution, and the organic layer was separated after vigorous stirring. This organic layer was washed with 6 N aqueous sodium hydroxide solution (5.9 mL), and dired over anhydrous magnesium sulfate. The solvent was evaporated under a reduced pressure to obtain the title compound (1.54 g. 66.9%). The title compound was used in the following reaction without being outflied.

[Manufacturing Example 11-1-2] Acetic acid 4-methyl-pyridin-2-ylmethyl ester

[0407]

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[0408] Acatic anhydride (30 mL) was added to 2,4-dimethyl-pyridine 1-oxide (1.93 g, 15.7 mmol) described in Manufacturing Example 11-1-1, and the mixture was stirred for 10 minutes at 110°C. The reaction solution was allowed to room temperature and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography (heptane: ethyl acetate = 1:2, then ethyl acetate) to obtain the title compound (774 mg, 29.8%).

1H-NNR Spectrum (DMSO-d₀) 8 (ppm): 211 (3H, s), 2.32 (3H, s), 5.09 (2H, s), 7.16 (1 H, d, J = 5.2 Hz), 7.23 (1 H, s), 8.39 (1 H, d, J = 5.2 Hz).

[Manufacturing Example 11-1-3] (4-Methyl-pyridin-2-yl)-methanol

[0409]

[0410] 5 N Aqueous sodium hydroxide solution (2 mL) and methanol (4 mL) were added to acetic acid 4-methylpyridin-2-ylmethyl ester (774 mg, 4.69 mmol) described in Manufacturing Example 11-1-2, and this mixture was stirred for 10 minutes at 60°C. The reaction solution was partitioned into water and ethyl acetate. The separated aqueous layer was further extracted with ethyl acetate twice. The ethyl acetate layers were combined and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure to obtain the title compound (410 mg, 71.0%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.32 (3H, s), 4.52 (2H, brs), 5.35 (1 H, brs), 7.06 (1 H, d, J = 5.2 Hz), 7.29 (1 H, s), 8.32 (1 H, d, J = 5.2 Hz).

[Manufacturing Example 11-1-4] 2-Chloromethyl-4-methyl-pyridine

[0411]

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[0412] A mixture solution of (4-methyl-pyridine-2-yl)-methanol (410 mg, 3.33 mmol) described in Manufacturing Example 11-1-3, thioryl chloride (0.49 ml, 6.66 mmol) and methylene chloride (10 ml, by as stirred under reflux for 5 minutes. The reaction solution was allowed to room temperature and concentrated under a reduced pressure. The resulting residue was partitioned into diethyl either and saturated sodium bicarbonate solution. The organic layer was purified by silica gel column chromatography (ethyl acetate) to obtain the title compound (440 mg, 72.1 %).

1H-NNR Spectrum (DMSO-d₀) 5 (ppm): 2.37 (3H, s), 4.72 (2H, s), 7.20 (1 H, d, J = 5.2 Hz), 7.38 (1 H, s), 8.40 (1 H, d, J = 5.2 Hz).

25 [Example 12] 3-(3-(6-Benzyloxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0413]

NH₂

[0414] To a solution of 3-ethynyl-pyridin-2-ylamine (400 mg, 3.99 mmol) described in Marufacturing Example 1:2-8 in anhydrous tetharpidrotura (0.00 mg) was added (2-benzylosy-pyridin-5-yl-acethydrotura) (0.5 50, g. 9.03 mmol) under nitrogen atmosphere at room temperature. Triethylamine (1.89 mt, 13.6 mmol) was then added droowise hereto, and stirred for 1.5 hours at room temperature. The reaction mixture was partitioned into water and ethyl acetate at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride, and dired over anhydrous magnesium suifate, and the solvent was evaporated under a reduced pressure. The retaidue was purified by his islicage (comm chromotography (ethylacetate 1: heptane = 1: 59then 1: 2)to obtain the title compound (315 mg, 26%). Hi-NMR Spectrum (DMSO-d₀) 8 (ppm): 4.00 (2H, e), 5.34 (2H, e), 6.27 (2H, br.), 6.70 (1H, dd, 4 = 8.4 T, 6.1+2), 6.84 (1H, dd, 3 = 8.4 T, 6.71-7.44 (5H, m), 7.98 (1H, dd, 3 = 2.4, 8.4 Hz), 7.87 (1H, dd, 3 = 2.0, 7.4 Hz), 8.09 (1H, dd, 3 = 2.4, 4.8 Hz), 8.17 (1H, d, 3 = 2.4 Hz).

[Manufacturing Example 1 2-1 -1] 2-Benzyloxy-5-bromopyridine

[0415]

[0416] To a solution of phenyl-methanol (20.5 g, 190 mmol) in NN-dimethylformamide (200 mL) was added sodium hydride (7.6 g, 190 mmol) under introgen atmosphere on an ice bath (PC), which was stirred for 30 minutes at room temperature. 2.5-Dibromopyridine was then added thereto on the ice bath (0°C), nad stirred for 60 minutes at room temperature. The reaction mixture was partitioned into water and ethyl acetate on the ice bath (0°C). The original leyer was washed with water and saturated aqueous sodium chindrie, and dried over antifyrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by silice gel column chromatography (ethyl acetate: heptane = 1: 20 then 1: 10) to obtain the title compound (16.1 g, 90%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.34 (2H, s), 6.71-6.73 (1 H, m), 7.32-7.45 (5H, m), 7.64-7.67 (1H, m), 8.20-8.21 (1 H, m).

[Manufacturing Example 12-1-2] 6-Benzyloxy-pyridin-3-carbaldehyde

[0417]

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[0418] To a solution of 2-benzyloxy-5-bromopyritine (15.1 g, 57.0 mmb) described in Manufacturing Example 12-1-1 in anhydrous tetrahydrotran (250 ml.) were added dropwise n-butyll filthium (2.67 M n-hexame solution, 25.6 ml., 86.4 mmb) under integen atmosphere on a dry ice-ethanol beth (78°C), which was stirred for 30 minutes. Yafe'C. An Dimetrylformamide (6.60 ml., 85.5 mmol) was then added thereto at -78°C, and stirred for 30 minutes. Water and ethyl caetate were added to the reaction mixture, and the organic layer was separated after stirring for 10 minutes at room temperature. The organic layer was weshed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was exporated under a reduced pressure. The residue was purified by NH silics age (column chornotography (ethyl acette: heptane = 1.7 men 1.5) to obtain the title compound (4.87 g., 40%).

14-MNB Spectrum (CDCl₂) 5 (ppm): 5.49 (2H, s), 6.89-6.92 (1 H, m), 7.34-7.48 (6H, m), 8.07-8.10 (1 H, m), 8.64-8.65 (1 H, m), 9.71 (1 H, s).

[Manufacturing Example 12-1-3] 2-Benzyloxy-5-((E)-2-nitro-vinyl)-pyridine

[0419]

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[0420] To a solution of 6-benzyloxy-pyridin-3-carbaldehyde (4.87 g, 22.8 mmol) described in Manufacturing Example 12-1-2 in acetic acid (30 mL) were added nitromethane (6.96 g, 114 mmol) and ammonium acetate (3.51 g, 45.6 mmol)

under nitrogen atmosphere at room temperature, which was stirred for 2.5 hours at 110°C. The reaction mixture was partitioned into water and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure to obtain the title compound (5.60 0.96%) as a crude oroduct.

1H-NMR Spectrum (DMSO-d_e) δ (ppm): 5.43 (2H, s), 7.01 (1H, d, J = 8.8 Hz), 7.34-7.47 (5H, m), 8.16 (1 H, d, J = 13.6 Hz), 8.24 (1 H, d, J = 13.6 Hz), 8.27 (1H, dd, J = 2.4, 8.8 Hz), 8.64 (1 H, d, J = 2.4 Hz).

[Manufacturing Example 12-1-4] 2-Benzyloxy-5-(2-nitro-ethyl)pyridine

[0421]

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[0422] To a solution of 2-benzyloxy-5-((E)-2-nitro-vinyl)-pyridine (6.80 g. 2.8 mmol) described in Menufacturing Exmple 12-13 and actica celd (6.8 mM) in dimethyl sulcoide (70 mL) was added sodium borbydride (1.4.6 g. 36.2 mmol) under nitrogen atmosphere at room temperature while cooling appropriately, which was stirred for 10 minutes at room temperature. The reaction mixture was partitioned into water and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chioride, and dried over antivous magnesium suifate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 1: 41 to obtain the title compound (2.50 g. 43%).

¹H-NMR Spectrum (DMSO- d_0) δ (ppm): 3.17 (2H, t, J = 6.8 Hz), 4.84 (2H, d, J = 6.8 Hz), 5.31 (2H, s), 6.84 (1 H, d, J = 8.4 Hz), 7.31-7.42 (5H, m), 7.68 (1 H, dd, J = 2.4, 8.4 Hz), 8.06 (1 H, d, J = 2.4 Hz).

[Manufacturing Example 12-1-5] (2-Benzyloxy-pyrldin-5-yl)-acetohydroximoyl chloride

[0423]

[0424] To a solution of 2-benzyloxy-5-[2-nitro-ethylpypridine (3.97 g, 15.4 mmol) described in Manufacturing Example 12-14 in methanol (25 mL) was added lithium embtoxide (1.17 g, 3.0.8 mmol) under nitrogen etrassphere at room temperature, which was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under a reduced pressure. Anhydrous metrylene chloride (30 mL) and anhydrous tetrahydrofuran (20 mL) were added to the residue. Tilanium (IV) chloride (5.42 mL, 49.3 mmol) was added dropwise into the reaction mixture on a dry loce-thianol bath (78°C), and stirred for 45 minutes at 0°C. Water, ethyl acetate and tetrahydrofuran were added to the reaction mixture on an oie bath (0°C), and the organic layer was separated. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure to obtain the title commount (3.4 a, 80%) as a crude product.

 1 H-NMR Spectrum (DMSO-d₀) δ (ppm): 3.79 (2H, s), 5.34 (2H, s), 6.87 (1 H, d, J = 8.4 Hz), 7.30-7.62 (5H, m), 7.61 (1 H, dd, J = 2.4, 8.4 Hz), 7.08 (1 H, d, J = 2.4 Hz), 11.8 (1H, s).

55 [Example 13] 3-(3-(4-Benzyloxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[0425]

[0426] To a mixture of 4-benzyloxy-phenyl-seatohydroximoyi chloride (140 mg, 0.51 mmol) described in Manufacturing Example 11-13 and tetrahydrofuran (10 mL) were added 3-ethynyl-pyridin-2,6-diamine (102 mg, 0.78 mmol) described in Manufacturing Example 13-13-and triethylemine (0.71 mL, 5.1 mmol), which was stirred overnight at room temperature. The reaction mixture was then stirred for further 1.5 hours at 55°C. The reaction solution was cooled to room temperature and concentrated under a reduced pressure. The residue was filtered by NH silliage glo column chromatography (ethyl acetals) to obtain a crude product. The crude product was purified by reverse-phase high performance liquid chroma-comply (using an acetonitrile-water mobile phase containing 0.1 % trifluoroacetic acid). The solvent was evaporated under a reduced pressure, and the residue was filtered with NH silica gel to obtain the title compound (51 mg, 27%).

14-NHM Spectrum (DMSC-Q₃) 6 (ppm): 3.87 (2H, s), 5.07 (2H, s), 5.79 (2H, brs), 5.82 (1H, d, J = 8.6 Hz), 6.10 (2H, brs), 6.34 (1H, d, J, 6.94-6.8) (2H, m), 7.20-7.24 (2H, m), 7.30-7.45 (6H, m), 7.51 (1H, d, J = 8.4 Hz).

The starting material, 3-ethynyl-pyridin-2,6-diamine, was synthesized as follows. [Manufacturing Example 13-1-1] 3-lodo-pyridin-2,6-diamine

5 [0427]

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[0428] 2.6-Diaminopyridine (100 g, 916 mmol) was dissolved in dimethyl sulfoxide (400 mL), and N-lodosucchimide (100 g, 445 mmol) was added in one portion while stirring at room temperature. The reaction solution was stirring for 10 minutes at room temperature. Water (3.5 L) was added to the reaction solution, and the precipitated solids were filtered out. The resulting aqueous layer was extracted with ethyl acetate (1.3 L) 3 times. The ethyl acetate layers were combined and the solvent was everyonated under a reduced pressure. The residue was purified by silting api chromatography (heptane: ethyl acetate = 2: 3) to obtain the title compound (23.8 g, 22.8%).

11-NMR Spectrum (DNSO-d_4) 5 (pm): 5.41 (H, hp. 5.57 (H, d_4) = 8.0 Hz), 5.44 (H, hps), 7.37 (H, d_4) = 8.0 Hz).

[Manufacturing Example 13-1-2] 3-Trimethylsilanylethynyl-pyridin-2,6-diamine

[0429]

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[0430] To a mixture of 3-iodo-pyridin-2.6-diamine (20.0 g, 85.2 mmol) described in Manufacturing Example 13-1-1,

trimethysisyl acetylene (24.2 mL, 170 mmol), copper (I) iodide (3.25 g, 17.0 mmol) M,M-discoproylethylemine (19.1, a 148 mmol) and M-methylyprodificione (28 mL) was added tetraksityfrohepythospholepyladaulum (0) (8.1 g), 8.6 2 mmol) under argon atmosphere, which was stirred for 30 minutes at room temperature. The reaction solution was partitioned into water and ethyl acetate. The ethyl acetate leyer was versided with water 4 times and dried over sodium sulfate, and the solvent was exerporated under a reduced pressure. The residue was purified by M silica gel chromatography (heptane : ethyl acetate = 4: 1 then 1: 1). The solids obtained by concentrating the elutar under a reduced pressure were washed with heptane containing a small amount of ethyl acetate to obtain the title compound (10.5 g, 60.0%). 11-NMR Spectrum (DMSO-d₀) 8 (ppm): 0.20 (9H, s), 5.53 (2H, brs), 5.88 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 5.95 (2H, brs), 7.11 (1 H, d, J = 8.0 Hz), 7

[Manufacturing Example 13-1-3] 3-Ethynyl-pyridin-2.6-diamine

[0431]

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[0432] To a solution of 3-trimethylsilanylethynyl-pyridin-2,6-diamine (7.0 g, 3.1 mmol.) described in Manufacturing Example 13-1-2 in tetrahydrduran (100 ml.) was added tetrabulylammonium fluoride (1M tetrahydrofuran solution, 17 ml., 17 mmol) on an ice bath, which was stirred for 10 minutes at room temperature. Water was added to the reaction solution, which was then extracted with ethyl acetate 3 times. The extract was dried over sodium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate) to obtain the title compound (3.35 g, 73.6%).

 1 H-NMR Spectrum (DMSO-d₆) δ (ppm): 4.08 (1 H, s), 5.57 (2H, brs), 5.68 (1 H, d, J = 8.0 Hz), 5.89 (2H, brs), 7.14 (1 H, d, J = 8.0 Hz).

[Example 14] 3-(3-(4-Pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridine-2,6-diamine

[0433]

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[0434] To a solution of 3-ethynyl-pyridin-2-d-dismine (120 mg, 0.90 mmol) described in Nanufacturing Exemple 181-18 and 4-(pyridin-2-ylonymethyl-phenyl-acetohydroximyot chloride (390 mg, 1.4 t mmol) described in Nanufacturing Exemple 2-1-5 in tetrahydroturan (6.0 mL) was added triethylamine (602 µL, 3.6 mmol) at 0°C. The reaction mixture was stirred for 1 hour and 30 minutes at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separately, washed with water and saturated aqueus sodium chloride, and dired over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gla column chromatography (heptane: ethyl acetate = 1:1, then ethyl acetate to toobtain the title compound (290 mg, 86.2%). 1-1-NMR Spectrum (DMSO-q.) & (ppm): 3.95 (2H, s), 5.31 (2H, s), 5.79 (2H, brs), 5.26 (1H, d, J = 8.4 Hz), 7.97 (3H, m), 6.18-18 (1H, m).

[Example 15] 3-(3-(4-(6-Methyl-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[0435]

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[0436] To a solution of 3-ethynyl-pyridin-2,6-diamine (900 mg. 2.5 mmol) described in Manufacturing Exemple 13-13 in an hydrous startarylarduran (30 mL) was added (4-(6-methyl-pyridin-2-yloxymethyl-phenyl)-castohydroximoyi chlorida (1.50 g. 5.15 mmol) described in Manufacturing Exemple 3-1-5 under nitrogen atmosphere at room temperature. Triethyamine (1.25 mL, 9.00 mmol) was then added dropwise at room temperature, and stirred for 1.5 hours at room temperature. Water and ethyl accetate were added to the reaction mixture at room temperature, and the organic layer was separated. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over analydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH allica gel column chromatography (ethyl acetate: heptane-2: 1) to obtain the title compound (637 mg, 73%).

11-MMR Spectrum (DMSO-dyl 6 ppm; 2.30 GH, 19, 3.86 QH, 19, 5.26 QH, 19, 5.80 GH, 19, 5.83 CH, 14, 5.16 LH, 5.11 (2H, 1.5 T, 16 H, 4.1 J, 5.81 H, 4.1 J,

[Example 16] 3-(3-(4-Butoxymethyl-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[0437]

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[0438] To a solution of 3-ethynyl-pydin-2_c-diamine (14.6 mg. 0.11 mmol) described in Manufacturing Example 13-13-4 and 4-butosymethy-phenyl-actohydxoxinoyl-choine(2.6 mg. 0.11 mmol) described in Manufacturing Example 4-14 in tetrahydrofuran was added triethylamine (31 μ L, 0.22 mmol), which was stirred for 4 hours at room temperature. The reaction solution was partitioned into water and ethyl sociate at room temperature. The organic hislay was a washed with securated aqueous solution choined and dried over anhydrous magnesium suifate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica get column chromatography (heptane : ethyl acetate 2 : 1) and then purified again by reverse-phase high performance figuid chromatography (heptane) an acetohrifier water mobile phase containing 0.1% influoroacetic acid to obtain the title compound (6.7 mg. 13%) as a trifluoroacetic acid salt. MS r/w (ESI) 563.34 (MHY)

[Example 17] 3-(3-(4-Phenoxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[0439]

[0440] To a solution of 3 ethynyl pyridin-2,6 diamine (170 mg, 28 mmol) described in Manufacturing Example 13-13 in anhydrous letrahydrofuran (10 mL) was added (4-phenoxy-bercare)-acetohydroximoyl choinde (652 mg, 2.9 mmol) described in Manufacturing Example 17-14 under nitrogen atmosphere at room temperature. Triethylamine (714 µL, 5.12 mmol) was then added dropwise, and stirred for 1 hour at room temperature. The reaction mixture was partitioned into water and ethyl acetate at room temperature. The organic layer was washed with water and saturated aqueous sodium chioride, and dried over arrhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1: 2 then 2: 1) to obtain the title compound (341 mt, 685%).

¹H-NMR Spectrum (DMSO-d_e) δ (ppm): 4.00 (2H, s), 4.74 (2H, brs), 5.50 (2H, brs), 5.94 (1 H, d, J = 8.8 Hz), 6.03 (1 H, s), 6.9F-7.02 (2H, m), 7.08-7.12 (1 H, m), 7.22-7.28 (5H, m), 7.30-7.35 (1 H, m), 7.52 (1 H, d, J = 8.8 Hz). The startine material. (4-henoxy-betzene)-acetohydroximovi olhoride, was synthesized as follows.

[Manufacturing Example 17-1-1] Sodium 2-nitro-1-(4-phenoxy-phenyl)-ethanolate

25 [0441]

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48 [0442] To a solution of 4-phenoxybenzaldehyde (1.5 g, 7.56 mmpl) in methanol (12 mL) was added dropwise sodium methoxide (1.49 M methanol solution, 0.19 mL, 0.31 mmol) under nitrogen atmosphere at room temperature. Nitromethane (530 µL, 9.84 mmol) was added dropwise to the reaction solution on an ice bath (0°C). Sodium methoxide (1.48) methanol solution, 1.66 mL, 8.16 mmol) was added dropwise thereto at room temperature, and the solution was stirred for 30 minutes at room temperature. The precipitated solids were filtered and ried under reduced pressure, and the solids were dried azeotropically with toluene to obtain the title compound (1.17 g, 55%).

1H-NNR Spectrum (DMSO-d₃) 6 (pm); 5.38 (1 H, m), 5.73 (1 H, d, J = 5.2 Hz), 6.58 (1 H, d, J = 4.4 Hz), 6.91-7.00 (4H, m), 7.09-7.13 (1 H, m), 7.47-7.39 (4H, m).

[Manufacturing Example 17-1-2] 1-((E)-2-Nitro-vinyl)-4-phenoxy-benzene

[0443]

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[0444] A solution of sodium 2-nitro-1-(4-phenoxy-phenyl)-ethanolate (1.17 g. 4.16 mmol) described in Manufacturing Example 17-1-1, acstic anhydride (510 mg. 4.99 mmol) and thethylamine (696 µL, 4.99 mmol) in anhydrous tethalydrofuran (20ml), was stirred overnithin under nitrosen antiposhera tet room temperature. The reaction mixture was partitioned

into water and ethyl acetate at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure to obtain the title compound (14, 20%), curity, ca. 50%) as a crude product.

5 [Manufacturing Example 17-1-3] 1-(2-Nitro-ethyl)-4-phenoxy-benzene

[0445]

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[0.446] To a solution of 1-f(E)-2-ritro-vinyl-4-phenoxy-berzene (1.40 g. 2.80 mmol, purity; 50%) described in Manufacturing Example 17-1-2 in methanol (15 mL) was added sodium borohydride (274 mg, 7.25 mmol) at room temperature while cooling appropriately under ritrogen atmosphere, which was stirred for 10 minutes at room temperature. Water was then added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with ethylacetate. The organic layer was washed with water and saturated equeous sodium-chroide, and drideover anhydrous magnesium sulfate, and the solvent was everyorated under a reduced pressure. The residue was purified by silica gel column chromatography (leth) sectate: heptane = 1-5 (b) tooblan the title compound (19 mg, 28%). 1H-MMR Spectrum (DMSO-d₃) 8 (ppm): 32 (2H, t, J = 6.8 Hz), 4.84 (2H, t, J = 6.8 Hz), 6.94-7.00 (4H, m), 7.11-7.15 (1 H, m), 7.28-7.30 (2H, m), 7.36-7.00 (2H, m).

[Manufacturing Example 17-1-4] (4-Phenoxy-benzene)-acetohydroximoyl chloride

[0447]

[0448] To a solution of 1-(2-nitro-ethy)4-phenoxy-benzene (100 mg, 0.41 mmol) described in Manufacturing Example 171-3.1 m rehand of mn.) was added sodium methods (1.48 M methand solution, 83 g. bg., 0.41 mmol) under nitrogen atmosphere, which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. Anhydrous methylene chloride (3 ml.) was added to the residue. Thanium (IV) chloride (54 2 μ.), 0.48 mmol) was added dropwise to the reaction mixture on an ice bath (0°C) and stirred for 30 minutes at room temperature. Water, ethyl acotate and tuterhydrofuram were added on the ice bath (0°C) to partition the reaction mixture. The organic size years was washed with water and saturated aqueues sodium chloride, and dried over enhydrous magnesis musuffact, and the solvent was exponented under a reduced pressure. The residue was purified by slica gel column chromatography (ethyl acotate 1: beptane = 1: 5) to obtain the title compound (51 mg, 47%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.80 (2H, s), 6.96-7.03 (4H, m), 7.12-7.16 (1 H, m), 7.26-7.28 (2H, m), 7.36-7.41 (2H, m), 11.7 (1 H, s).

[Example 18] 3-(3-(4-(2-Fluoro-benzyloxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

50 [0449]

[0450] To a solution of 4.6;12.6 diamino pyridin-3-yl)-isovazo-3-ylmethyl-) phonol (72.4 mg. 0.28 mmol) described in Manufacturing Exemple 18-1-1 in tertahydrofuran (3 mL) was added 5 N aqueous sodium hydroxide solution (51.2 µL, 0.26 mmol), which was irradiated by ultrasonic wave for 5 minutes. Next, the reaction solution was concentrated under a reduced pressure to obtain soluds (77.9 mg.) To a solution of the resulting solids (14.5 mg. 0.05 mmol) in N,N-dimethylfornamide (1 mL) was added 2-fluoroberaryl bromde (11.5 µL, 0.10 mmol), which was stirred for 2 hours at room temperature. The reaction solution was partitioned into water and ethyl acetate. The organic layer was washed with water and startised aqueous solution chlorids, and dried over anhylfoxus magnesium sultale, and the sovent was everporated under a reduced pressure. The residue was purified by slice gel column chromatography (ethyl costats) and then further purified by reverse-phase high performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % influoroacetic acid sait.

1H-NMR Spectrum (CDCl₃) (opm); 3.96 (2H, s), 4.57 (2H, brs), 5.12 (2H, s), 5.90 (2H, brs), 5.91 (1 H, d, J = 8.4 Hz), 7.69-7.11 (1H, m), 7.14-7.24 (1 H, m), 7.20 (2H, d, J = 8.4 Hz), 7.69-7.51 (1H, m), 7.49 (1H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7.24 (1H, m), 7.20 (2H, d, J = 8.4 Hz), 7.49-7.51 (1H, m), 7.49-7

[Manufacturing Example 18-1-1] 4-(5-(2.6-Diamino-pyridine-3-vl)-isoxazol-3-vlmethyl)-phenol

[0451]

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[0452] To a solution of 3-(3-44-benzyloxy-benzyl)-isoxz20-f-5yl)-pyridin-2,6-diamine (100 mg, 0.27 mmol) described in Example 13 in trilluroraceotic acid (3 mL) was added thioanisole (126 μ L) at room temperature. Sutherated aqueous sodium hydrogen carbonale solution was added to the reaction solution at 0°C, which was then extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous megnesium sutilate, and the solvent was evaporated under areduced pressure. The residue was purified by slice gel column chromatography (ethyl acetate) to obtain the title compound (72-4 mg, 95%). H-NMR Spectrum (DMSO-Q₃) 5 (ppm): 3.82 (2H, s), 5.79 (2H, brs), 5.83 (1 H, d, J = 8.4 Hz), 9.27 (1H, d, J = 8.4

[Example 19] 3-(3-(4-(3-Fluoro-benzyloxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[0453]

[0454] To a solution of 4-(5-(2.6-diamino-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol (72.4 mg, 0.26 mmol) described in Manufacturing Example 18-1-1 in tetrahydrofuran (3 mL) was added 5 N aqueous sodium hydroxide solution (51.2 u.L. 0.26 mmol), which was irradiated by ultrasonic wave for 5 minutes. Next, the reaction solution was concentrated under a reduced pressure to obtain solids (77.9 mg). To a solution of the resulting solids (11.3 mg, 0.04 mmol) in N,N-dimethylformamide (1 mL) was added 3-fluorobenzyl bromide (9.1 µL, 0.07 mmol), which was stirred for 2 hours at room temperature. The reaction solution was partitioned into water and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate), and further purified by reverse-phase high performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (6.7 mg, 36%) as a trifluoroacetic acid salt.

MS m/e (ESI) 391.34 (MH+)

[Example. 20] 3-(3-(4-(4-Fluoro-benzyloxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[0455]

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[0456] To a solution of 4-(5-(2,6-diamino-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol (72.4 mg, 0.26 mmol) described in Manufacturing Example 18-1-1 in tetrahydrofuran (3 mL) was added 5 N aqueous sodium hydroxide solution (51.2 µL, 0.26 mmol), which was irradiated by ultrasonic wave for 5 minutes. Next, the reaction solution was concentrated under a reduced pressure to obtain solids (77.9 mg). To a solution of the resulting solids (13.7 mg, 0.05 mmol) in N,N-dimethylformamide (1 mL) was added 4-fluorobenzyl bromide (11.2 μL, 0.09 mmol), which was stirred for 2.5 hours at room temperature. The reaction solution was partitioned into water and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate), the mixture was purified by reverse-phase high performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trifluoroacetic acid) and then purified by preparative thin-layer chromatography (ethyl acetate : hexane =1:1) to obtain the title compound (4.0 mg, 18%).

¹H-NMR Spectrum (CDCl₂-d₅) δ (ppm): 3.96 (2H, s), 4.53 (2H, brs), 5.00 (2H, s), 5.30 (2H, brs), 5.91 (1H, d, J = 8.0 Hz), 5.98 (1 H, s), 6.92 (2H, dd, J = 2.0, 6.8 Hz), 7.05-7.15 (2H, m), 7.20 (2H, d, J = 8.4 Hz), 7.26-7.46 (2H, m), 7.48 (1 H. d. J = 8.0 Hz).

MS m/e (ESI) 391.04 (MH+)

[Example 21] 3-(3-(4-Cyclopropylmethoxy-benzyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[0457]

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[0488] To a solution of 4-(6-(2.6 diamino pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol (72.4 mg, 0.26 mmol) described in Manufacturing Example 18-1-1 in tetrahydrotura (3 ml) was added 5 N aqueus sodium hydroxide solution (51.2 µL, 0.26 mmol), which was irrediated by ultrasonic wave for 5 minutes. Next, the reaction solution was concertated under a reduced pressure to obtain solids (7.79 mg). To a solution of the resulting solids (8.3 mg, 0.03 mmol) in NN-dimethydromamide (1 mL) was added cyclopropylmethyd bromide (5.3 µL, 0.06 mmol), which was stirred for 5 hours at room temperature. The mixture was purified by reverse-phase high performance liquid chromatography (using an acetontrile-water mobile phase containing 0.1 % trifluoroacetic acid), and then further purified by preparative thin-layer chromatography (taking at this compound (11 mg, 12%).

1H-1MR Spectrum (CDCL₃-d₆) δ (ppm): 0.33-0.36 (2H, m), 0.63-0.66 (2H, m), 1.24-1.29 (1 H, s), 3.79 (2H, d, J = 4.8 Hz), 3.96 (2H, s), 4.57 (2H, b), 5.34 (2H, bn), 5.92 (1 H, d, J = 8.4 Hz), 5.99 (1 H, s), 6.87 (2H, dd, J = 2.0, 6.8 Hz), 7.19 (2H, dd, J = 2.0, 6.8 Hz), 7.49 (1 H, d, J = 8.4 Hz).

MS m/e (ESI) 3.37.11 (MHY)

[Example 22] 3-(3-(4-(Pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[0459]

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[0460] To a solution of 4-(6-2,6-diamino-cyndin-3-yh-lacoxac-0-3-yinethyl)-phenol (49,7 mg, 0.18 mmol) described in Marufacturing (Example 18-1-1 in tetrahydrofura of kind) was added 58 naqueous sodium hydroxide solution (38.2 µL, 0.18 mmol), which was irradiated by ultrasonic wave for 5 minutes. Next, the reaction solution was concentrated under a raduced pressure to obtain solids (9.6 mg). The resulting solids were made into an Ni-dimethyldromanitie (3 mL) solution. Tetrahydrofuran (390 µL) and 1 N aquaeous sodium hydroxide solution (390 µL, 0.39 mol) were added to 2-picelyl chloride hydrochloride (50 mg, 0.39 mmol), and then the organic layer was separated to obtain tetrahydrofuran solution of 2-picelyl chloride. A part of the solution (0.30 mL) was added to the altorementioned N,N-dimethylformanide solution, and stirred for 15 hours at room therpeature. The reaction solution was partitioned into water and ethyl societat. The organic layer was washed with water and saturated reaction solution molified, and office over anythrous magnesium sulfate, and the solver was washed with water and saturated reaction solution residue was purified by silica gel column chromatography (ethyl acetate) to obtain the title compound (42.5 mg, 39%).

1H-NMR Spectrum (DMSO-q_e) δ (ppm): 3.88 (2H, s), 5.15 (2H, s), 5.79 (2H, brs), 5.83 (1 H, dd, J = 1.2, 8.4 Hz), 6.11 (2H, brs), 6.36 (1 H, s), 6.97 (2H, d, J = 8.0 Hz), 7.22 (2H, d, J = 8.4 Hz), 7.33 (1 H, dd, J = 5.2, 8.0 Hz), 7.49 (1 H, d, J = 8.0 Hz), 7.51 (1 H, d, J = 8.0), 7.82 (1 H, dd, J = 8.0, Rz), 7.51 (1 H, dd, J = 8.0, Rz), 7.51 (1 H, dd, J = 8.0, Rz), 7.52 (1 H, dd, J = 8.0, Rz), 7.52 (1 H, dd, J = 8.0, Rz), 7.53 (1 H, dd, J = 8.0, Rz), 7.53 (1 H, dd, J = 8.0, Rz), 7.54 (1 Hz), 7

[Example 23] 3-(3-(4-(6-Methyl-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[0461]

[0462] To 4-(5-(2.6 diamino-pyridin-3-yf)-isoxazol-3-y/methyf)-phenol (150 mg, 0.53 mmol) described in Manufacturing Example 18-1-1 were added methanol (3 ml.) and 1 N aqueous sodium hydroxide solution (0.53 ml.), which was then dissolved by Irrediating ultrasonic wave. This solution was concentrated under a reduced pressure. To the resulting residue was added 2-chiloromethyl-6-methyl-pyridine (90.2 mg, 0.64 mol.) described in manufacturing Example 10-1-1 and N,N-dimethylformamide (2 ml.), which was stirred for 2 hours and 50 minutes at 60°C. The reaction solution was purificioned into vater and ethyl acetate. The organic layer was evaporated under a reduced pressure. The residue was purified by NH silics gel column chromatography (heptane: ethyl acetate = 1: 2, then ethyl acetate) to obtain the title compound (106 m. 5.1.5%).

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.48 (3H, s), 3.88 (2H, s), 5.10 (2H, s), 5.78 (2H, brs), 5.82 (1 H, d, J = 8.4 Hz), 6.10 (2H, brs), 6.34 (1H, s), 6.36 (2H, d, J = 8.0 Hz), 7.16 (1 H, d, J = 8.0 Hz), 7.22 (2H, d, J = 8.0 Hz), 7.27 (1 H, d, J = 8.0 Hz), 7.20 (1 H, d, J = 8.0 Hz), 7.27 (

[Example 24] 3-(3-(4-(4-Methyl-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

5 [0463]

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[0464] To 4-(5-(2,6-diamino-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol (80 mg, 0.28 mmol) described in Manufacturing Example 18-1-1 were added methanol (4 ml.) and 1 N aqueous sodium hydroxide solution (0.28 ml.), which was the dissolved by irradiating ultrasonic wave. This solution was concentrated under a reduced pressure. To the resulting residue was added 2-chloromethyl-4-methyl-pyridine (50,9 mg, 0.36 mol.) described in Manufacturing Example 11-14 and N.N-dimethylformamide (3 ml.), which was stirred for 10 minutes at 60°C. The reaction solution was partitioned into water and ethyl acetate. The organic layer was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 1 : 2, then ethyl acetate) to obtain the title compound (40 mo. 36.5%).

1H-NMR Spectrum (DMSO- d_0) δ (ppm); 2.32 (3H, s), 3.88 (2H, s), 5.10 (2H, s), 5.79 (2H, brs), 5.82 (1 H, d, J = 8.4 Hz), 6.10 (2H, brs), 6.35 (1 H, s), 6.97 (2H, d, J = 8.0 Hz), 7.15 (1 H, d, J = 5.2 Hz), 7.22 (2H, d, J = 8.0 Hz), 7.34 (1 H, s), 7.50 (1 H, d, J = 5.4 Hz), 8.41 (1 H, d, J = 5.2 Hz).

[Example 25] 3-(3-(6-Benzyloxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[0465]

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[0466] To a solution of 3-ethynyl-pyridin-2,6-diamine (230 mg, 1.73 mmol) described in Manufacturing Example 13-1-3 in anhydrous tetrahydrofuran (20 mL) was added (2-benzyloxy-pyridin-5-yl)-acetohydroximoyl chloride (1.00 g. 3.61 mmol) described in Manufacturing Example 12-1-5 under nitrogen atmosphere at room temperature. Triethylamine (965 μL, 6.92 mmol) was added dropwise to the mixture and stirred for 1.5 hours at room temperature. The reaction mixture was partitioned into water and ethyl acetate at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 2:1) to obtain

¹H-NMR Spectrum (DMSO-d_e) δ (ppm); 3.92 (2H, s), 5.33 (2H, s); 5.81 (2H, brs), 5.83 (1 H, d, J = 8.4 Hz), 6.11 (2H, brs), 6.40 (1 H, s), 6.85 (1 H, d, J = 8.8 Hz), 7.31-7.39 (3H, m), 7.42-7.44 (2H, m), 7.52 (1 H, d, J = 8.4 Hz), 7.66 (1 H, dd, J = 2.4, 8.4 Hz), 8.14 (1 H, d, J = 2.4 Hz).

[Example 26] 3-(3-(4-Benzyloxy-benzyl)-isoxazol-5-yl)-6-methoxymethyl-pyridin-2-ylamine

[0467]

the title compound (470 mg, 73%).

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[0468] To a mixture of (4-benzyloxy-phenyl)-acetohydroximoyl chloride (19 mg, 0.069 mmol) described in Manufacturing Example 1-1-3 and tetrahydrofuran (1 mL) were added 3-ethynyl-6-methoxymethyl-pyridin-2-ylamine (8.6 mg, 0.053 mmol) described in Manufacturing Example 26-1-7 and triethylamine (15 µL, 0.11 mmol) at room temperature, which was stirred for 5.5 hours at room temperature. Water was added at room temperature to the reaction mixture, which was then extracted with ethyl acetate-tetrahydrofuran (3:2). The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 2:3) to obtain the title compound (8.8 mg, 41 %). 1H-NMR Spectrum (CDCl₂) δ (ppm): 3.47 (3H, s), 3.99 (2H, s), 4.42 (2H, s), 5.05 (2H, s), 5.50 (2H, brs), 6.23 (1 H, s), 6.82 (1 H. d. J = 7.9 Hz), 6.93-6.97 (2H. m), 7.18-7.22 (2H. m), 7.31-7.44 (5H. m), 7.72 (1 H. d. J = 7.7 Hz).

The starting material, 3-ethynyl-6-methoxymethyl-pyridin-2-ylamine, was synthesized as follows.

[Manufacturing Example 26-1-1] 2-Amino-6-chloro-nicotinic acid

[0469]

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[0470] A mixture of 2,6-dichloro-nicotinic acid (31 g, 0.14 mol) and 28% aqueous ammonia solution (200 mL) was stirred in a sealed tube for 10 hours at 135°C. This reaction solution was cooled to room temperature, and the excess ammonia gas was removed under a reduced pressure. Water was added to the residue to a total of 1000 mL, the mixture was cooled to 0°C, and cliric acid was added to a pH being about 6. The precipitated solids were filtered out to obtain the title compound (12 or 49%).

1H-NMR Spectrum (DMSO-d_e) δ (ppm): 6.63 (1 H, d, J = 8.1 Hz), 7.55 (2H, brs), 8.02 (1H, d, J = 8.1 Hz).

[Manufacturing Example 26-1-2] 2-Amino-6-chloro-nicotinic acid methyl ester

[0471]

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CI N NH,

Q (472) Concentrated sulfuric acid (25 mL) and 2-amino-6-chloro-nicotinic acid (4.3 g, 25 mmol) described in Manufacturing Example 28-11 were added to methanol (50 mL) on an ice bath, and stirred at 70°C for 5 hours. The reaction mixture was cooled and then neutralized by addition of aqueous sodium hydrogen carbonate (90 g) solution. The precipitated solids were filtered to obtain the title compound (3.2 g, 17 mmol, 68%).

1H-NMR Spectrum (CDCl₂) δ (ppm): 3.88 (3H, s), 6.62 (1 H, d, J = 8.2 Hz), 8.05 (1 H, d, J = 8.1 Hz).

[Manufacturing Example 26-1-3] Tributyl-methoxymethyl-stannane

[0473]

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[0474] To a mixture of diisopropylamine (9.4 ml., 67 mmol) and tetrahydrofuran (150 ml.) was added dropwise n-butyl illhium (2.4 ml. n-hexane solution, 25 ml., 61 mmol) at -78°C, which was stirred for 30 minutes at the same temperature. Tributylith hydride (16 ml., 61 mmol) was added dropwise to the reaction mixture at the same temperature, and stirred for 30 minutes at 0°C. The reaction mixture was cooled to -78°C, and chloromethyl methyl ether (4.5 ml., 61 mmol) was added dropwise thereit. The reaction mixture was gradually wermed to room temperature. Water was added to the reaction mixture, which was then extracted with diethyl ether. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by neutral silica gel column chromatography (ethyl acetate: heptane = 1:30) to obtain the title compound (18 g, 36%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 0.88-0.93 (15H, m), 1.26-1.35 (6H, m), 1.47-1.55 (6H, m), 3.30 (3H, s), 3.71 (2H, t, J = 6.8 Hz).

[Manufacturing Example 26-1-4] 2-Amino-6-methoxymethyl-nicotinic acid methyl ester

50 [0475]

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NH,

[0478] A mixture of Z-amino-6-chloro-nicotinic acid methyl ester (1.4 g, 7.6 mmo)) described in Manufacturing Example 26-12, tributyl-methoxymethyl-stannane (3.1 g, 9.1 mmo)) described in Manufacturing Example 26-13, tetraki(triphe-nyiphosphini-palladium (440 mg, 0.38 mmol) and N-methylpymolidinone (20 mL) was stimed for 3.5 hours at 130°C. The reaction mixture was cooled to room temperature, and aqueous potassium fluoride solution and ethyl acetate were added to the reaction mixture, which was then filtered through a Cellie gad. The organic layer was separated and washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by slicia gel column chromatography (ethyl acetate: heptane = 1: 2) to obtain the title compound (0.93 g, 63%). H-MMR Specificam (COCLa) (Spma): 347 (91 st, 0.38 (81 st, 0.4) et 12 (1.5 g), 574 (11 d, 0.4 p-71 byt.), 34 (14 ft, 0.4 g, 0.4 p-71 byt.).

10 [Manufacturing Example 26-1-5] (2-Aming-6-methoxymethyl-pyridin-3-yl)methanol

[0477]

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ОН

20 [0478] To a mixture of Bhium aluminum hydrids (80%, 220 mg, 4.6 mmol) and tetrahydrotrunan (5 mL) was added 2-amino-6-methoxymethyl-nicotinic acid methyl ester (300 mg, 1.5 mmol) described in Manufacturing Example 26-1-4 at 0°C, which was stirred for 20 minutes at the same temperature. An aqueous 28% ammonia solution was added drownies to the reaction mixture at 0°C. The mixture was warmed to room temperature and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (260 mg, 100%).

25 1H-NMR Spectrum (CDCl₃) δ (ppm): 3.45 (3H, s), 4.39 (2H, s), 4.62 (2H, s), 5.03 (2H, brs), 6.70 (1 H, d, J = 7.3 Hz), 7.31 (1 H, d, J = 7.5 Hz).

[Manufacturing Example 26-1-6] 2-Amino-6-methoxymethyl-pyridine-3-carbaldehyde

30 [0479]

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[0460] To a mixture of (2-amino-6-methoxymethyt-pyridin-3-yl)methanol (260 mg, 1.5 mmol) described in Manufacturing Example 26-1-5 and methylene chloride (15 mL) was added manganese dioxide (1.3 g, 15 mmol), which was stirred overnight at room temperature. The reaction mixture was filtered through a Cellite pad, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : heatane = 3.2 to todatin the lite compound (20 mg, 81%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 3.48 (3H, s), 4.44 (2H, s), 6.87 (1 H, d, J = 7.9 Hz), 7.82 (1 H, d, J = 7.7 Hz), 9.84 (1 H, s).

[Manufacturing Example 26-1-7] 3-Ethynyl-6-methoxymethyl-pyridin-2-ylamine

[0481]

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[0482] To a mixture of disopropylamine (0.15 mt, 1.1 mmol) and tetrahydrofuran (2 mt) was added dropwise n-butyl lithium (1.6 M n-hexane solution, 0.68 mt., 1.1 mmol) at -78°C, which was stirred for 30 minutes at that temperature. Trimethysityl diazomethane (2 M n-hexane solution, 0.50 mt, 0.99 mmol) was added to the reaction mixture at -78°C,

and stirred for 30 minutes at that temperature. A mixture of 2-mino-6-methoxymethyl-pyridine-3-carbaideryide (150 mg, 0.90 mmol) described in Manufacturing Example 26-1-6 and tetrahydrofuran (1.5 mL) was added dropwise to the reaction mixture was cooled to -78°C, and stirred for 30 minutes at 0°C. The reaction mixture was cooled to -78°C, and a mixture of acetic acid (0.10 mL) and tetrahydrofuran (1 mL) was added dropwise to the reaction mixture. This reaction mixture was gradually warmed to 0°C, and partitioned into value and ethyl acetae. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica sol column chronotocraphy (ethyl acetate) is rebatine = 2: 31 to obtain the title compound (73 m. p. 50%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.40 (1 H, s), 3.45 (3H, s), 4.39 (2H, s), 5.07 (2H, brs), 6.72 (1 H, d, J = 7.7 Hz), 7.58 (1 H, d, J = 7.5 Hz).

[Example 27] 6-Methoxymethyl-3-(3-(4-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0483]

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[0444] To a mixture of 4-(pyridin-2-yloxymethyl)-phenyl-acetohydroxmoyl-chloride (18 mg, 0.064 mmol) described in Manufacturing Szample 2-15-a flat trientylorumin (1 mL) were added 3-ethynyl-6-methoxymethy-y-philox-2-ytamine (8.6 mg, 0.053 mmol) described in Manufacturing Example 26-1-7 and triethylamine (15 μ L, 0.11 mmol), which was stirred for 2 hours at room temperature. The reaction mixture was partitioned into water and ethyl acetate at room temperature. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was everporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 2: 3) to botain the title compound (10 mg, 48%).

1H-NMR Spectrum (CDCL₃) δ (ppm): 3.47 (3H, s), 4.07 (2H, s), 4.44 (2H, s), 5.37 (2H, s), 5.56 (2H, brs), 6.25 (1H, s), 6.79-6.84 (2H, m), 6.87-6.91 (1 H, m), 7.30 (2H, d, J = 7.9 Hz), 7.44 (2H, d, J = 7.9 Hz), 7.57-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7.87-7.61 (1 H, m), 7.73 (1 H, d, J = 7.9 Hz), 7

Example 28] 5-(3-(4-Benzyloxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0485]

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[0.486] To a solution of 5-ethynyl-pyridin-2-ylemine (10 mg, 85 µmol) described in Manufacturing Example 28-1-3 and 4-benzyloxy-phenyl-acetohydroximoyl chloride (70 mg, 0.25 mmol) described in Manufacturing Example 1-1-3 in termydrofuran (2 mL) was added thethyfamine (38 µL, 0.25 mmol) at noon temperature, which was stirred for 3 hours and 40 minutes at room temperature. The reaction solution was partitioned into water and ethyl acetate at 0°C. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium suifate, and the solvent was evaporated under a reduced pressure. The residue was purified by reverse phase high performance liquid chromatography (using an acetohitric-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (1 mg, 3%) as a trifluoroacetic acid start.

MS m/e (ESI) 358.00 (MH+)
The starting material, 5-ethynyl-pyridin-2-ylamine, was synthesized as follows.

[Manufacturing Example 28-1-1] 2-Nitro-5-trimethylsilanylethynyl-pyridine

[0487]

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O N N SI

[0488] To a solution of 5-bromo-2-nitropyridine (1.00 g., 4.93 mmol) in N-methylopyrolidinone (20 mL) were added trimethylsiyi acetylene (1.39 mL, 9.85 mmol), tetrakist(riphenylphosphine)palladium (0) (114 mg, 985 µmol), copper (1) iodide (37.5 mg, 197 µmol) and N/N-dilasopropylethylamine (1.72 mL, 9.85 mmol) at room temperature, which was atimed under nitrogen atmosphere for 4 hours at 65°C. The reaction solution was partitioned into water and ethyl acetate at 6°C. The organic layer was washed with water and saturated aqueous sodium chloride, and dired over anhydrous magnesium sulfate, and the solvent was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl acetate = 6: 1) to obtain the title compound (490 mg, 45%).

11-NMR Spectrum (CDCL) § (opmo.) 228 B(H), s. 90.8-8.0 f (1. Hm,) 8.22 (1 H, J. = 8.4 Hz), 8.68 (1. H, J. = 2.0 Hz).

[Manufacturing Example 28-1-2] 5-Trimethylsilanylethynyl-pyridin-2-ylamine

[0489]

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HANN

Q (0490) To a solution of 2-nitro-5-trimethylsitanylethynyl-pyridine (405 mg, 1.84 mmol) described in Manufacturing Example 28-1-1 in technydrofuran (10 ml.) and water (5 ml.) were added in on powder (514 mg, 9.24 mmol) and ammonium chloride (197 mg, 3.69 mmol) at room temperature, which was stirred for 75 minutes at 70°C. The reaction solution was cooled to room temperature and filtered through a Celite pad, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl acetate = 1:1) to obtain the title compound (319 mg, 91 %).

¹H-NMR Spectrum (CDCl₂) δ (ppm): 0.237 (9H, s), 4.73 (2H, brs), 6.44 (1 H, d, J = 8.6 Hz), 7.51 (1H, dd, J = 2.2, 8.4 Hz), 8.19 (1H, d, J = 2.2 Hz).

[Manufacturing Example 28-1-3] 5-Ethynyl-pyridin-2-ylamine

[0491]

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H₂N N

[0492] To a solution of 5-trimethylsianylethynyl-pyridin2-ylamine (26 mg, 137 µmol) described in Manufacturing Example 28-1-2 in tetrahydrofuran (1 mL) and methanol (1 mL) was added potassium carbonate (37.9 mg, 274 µmol) at room temperature, which was stirred for 1 hour at room temperature. The reaction solution was partitioned into water and ethyl acetate at 0°C. The organic layer was washed with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was concentrated under a reduced pressure. The residue was purified by NH silica get column chromatography (hetpates : ethyl acetate = 1: 1) to obtain the title compound (16 mg, 99) and the solvent was purified by NH silica get column chromatography (hetpates : ethyl acetate = 1: 1) to obtain the title compound (16 mg, 99) and the solvent was the solvent wa

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.07 (1H, s), 4.73 (2H, brs), 6.46 (1H, d, J = 8.6 Hz), 7.53 (1 H, dd, J = 2.2, 8.6 Hz), 8.21 (1 H, s).

[Example 2913-(5-(4-Benzyloxy-benzyl)-isoxazol-3-yl)-pyridin-2-ylamine

0 [0493]

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NH₂

[0494] To a solution of 3-(5-(4-benzyloxy-benzyl)-isoxazol-3-yl)-5-chloro-pyridin-2-ylamine (50 mg, 0.13 mmol) described in Manufacturing Example 29-2-3 in N-methypyrrolidinone (2 mL) were added formic acid (7.3 µL, 0.19 mmol). Ny-dillosprophyribynaline (67 µL, 0.38 mmol) and tetralskit(phichyribposhiphe)paldialium (0) (15 mg, 13 µmol) under nitrogen atmosphere at room temperature, which was stimed for 2 hours and 20 minutes at 100°C. Water and ethyl acetate were added to the reaction solution at room temperature, which was then filtered through a Ceitle pad. The filtrate was partitioned into water and ethyl acetate. The organic layer was washed with saturated aqueous sodium chioride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by reverse-phase high performance liquid chromatography (using an acetonitine-water mobile phase containing 0.1 % trifluoroacetic acid) and then purified again by NH silica gel column chromatography (heptane: ethyl acetate = 11) to obtain the title compound (6 mg, 11 %).

1H-MMR Spectrum (CDCl₂) 8 (ppm): 4.07 (2H, s), 5.07 (2H, s), 6.24 (1 H, s), 6.34 (2H, brs), 6.67 (1 H, dd, J = 4.9, 7.5 Hz), 6.95-6.98 (2H, m), 7.20-7.23 (2H, m), 7.31-7.45 (5H, m), 7.66 (1 H, dd, J = 1.7, 7.5 Hz), 8.11 (1 H, dd, J = 1.7, 4.9 Hz). MS m/e (ES)) 583-20 (MHY)

The starting material, 3-(5-(4-benzyloxy-benzyl)-isoxazol-3-yl)-5-chloro-pyridin-2-ylamine, was synthesized as follows.

[Manufacturing Example 29-1-1] 2-Amino-pyridine-3-carbaldehyde oxime

[0495]

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[0496] To a solution of 2-amino-3-formylpyridine (1.00 g, 8.19 mmol) in pyridine (20 mL) was added hydroxylamine hydrochioride (854 mg, 12.3 mmol) at room temperature, which was stirred for 1 hoursand 40 minutes at room temperature. The reaction solution was partitioned into water and telly lacetale. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: methanol = 10:1) to obtain the title comound (951 mg, 85%).

¹H-NMR Spectrum (DMSO- d_6) δ (ppm): 6.60 (1 H, dd, J = 4.8, 7.3 Hz), 6.94 (2H, s), 7.55 (1 H, m), 7.96 (1 H, dd, J = 1.7, 4.8 Hz), 8.22 (1 H, s), 11.2 (1 H, s).

[Manufacturing Example 29-1-2] 2-Amino-5-chloro-N-hydroxypyridin-3-carboxyimidoyl chloride

[0497]

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5 [048] To a solution of 2-amino-pyridine-3-carbaldshyde oxime (951 mg, 6.33 mmol) described in Manufacturing Example 29-1-1 in NN-dimethylfomamids (20 mL) was adden N-chlorosuccinimide (22 g, 16 mmol) at corn temperature, which was stirred at room temperature for 5 hours and 30 minutes. The reaction solution was partitioned into water and etnyl accetate at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anthyrous magnesium suifate, and the solvent was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (hepane: ethyl acetate = 1:1) to obtain the title compound (249 mg, 17%).

¹H-NMR Spectrum (DMSO-d_s) δ (ppm): 7.24 (2H, brs), 7.91-7.92 (1H, m), 8.06-8.07 (1 H, m), 12:6 (1H, s).

[Manufacturing Example 29-2-1] (3-(4-Benzyloxy-phenyl)-prop-1-ynyl)-trimethylsilane

[0499]

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[0500] To a solution of trimethylsilyl acetylene (851 μ L, 6.02 mmol) in tetrahydrofuran (20 mL) was added ethyl magnesium bromide (3 M diethyl ether solution, 1.86 mL, 5.59 mmol) under nitrogen atmosphere at room temperature,

which was stirred for 40 minutes at 65°C. The reaction solution was cooled to room temperature, and copper (I) bromide (308 mg, 2.16 mmol) and 4-benzylosybenzyl chloride (1.00 g, 4.30 mmol) were added to the reaction solution and stirred for 8 hours and 45 minutes at 65°C. Saturated armonium chloride solution was added to the reaction solution at room temperature, which was then extracted with eithyl acetate. The organic layer was washed with saturated aqueous solution chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 30:1) to obtain the title compound [911 mo. 278-b).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 0.18 (9H, s), 3.59 (2H, s), 5.06 (2H, s), 6.92-6.95 (2H, m), 7.23-7.26 (2H, m), 7.30-7.34 (1 H, m), 7.36-7.40 (2H, m), 7.42-7.44 (2H, m).

Manufacturing Example 29-2-21 1-Benzyloxy-4-prop-2-ynyl-benzene

[0501]

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[0502] To a solution of (3/4-benzyloxy-phenyl)-prop-1-ynyl-threathy-islane (911 mg. 3.09 mmol) described in Manideaturing Exemple 23-e1 in methanol (20 md), was added potassium carbonate (684 mg. 6.18 mmol) are room temperature, which was stirred for 4 hours and 10 minutes at room temperature. The reaction solution was partitioned into water and ethyl acetate at room temperature. The organic layer was washed with saturated aqueous sodium chiloride and dried over enhydrous magnedism usulfate, and the solvent was exporated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl acetate = 20:1) to obtain the title compound (618 mo. 89%).

 1 H-NMR Spectrum (CDCl₂) (ppm): δ 2.16 (1 H, t, J = 2.4 Hz), 3.54 (2H, d, J = 2.4 Hz), 5.05 (2H, s), 6.91-6.94 (2H, m), 7.24-7.26 (2H, m), 7.29-7.43 (5H, m).

[Manufacturing Example 29-2-3] 3-(5-(4-Benzyloxy-benzyl)-isoxazol-3-yl)-5-chloropyridin-2-ylamine

[0503]

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[0504] To a solution of 2-emino-5-choro-N-hydroxypyridin-3-carboxymidoyi chloride (100 mg, 485 µmo) described in Manufacturing Example 29-1-2 in diethyl ether [2 mL) and tetralytopicum (1 mL) were added 1-bezryoxy-4-prop-2-yry)-bezcene (113 mg, 509 µmo)) described in Manufacturing Example 29-2 and triethylamine (31 µL, 582 µmo)), which was stirred for 4 hours and 5 minutes at room temperature. The reaction solution was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 5: 1) to obtain the title compound (55 ms. 31 %).

¹H-NMR Spectrum (DMSO- d_6) δ (ppm): 4.11 (2H, s), 5.07 (2H, s), 6.97-6.99 (3H, m), 7.05 (2H, s), 7.24 (2H, d, J = 8.6,Hz), 7.29-7.32 (1 H, m), 7.37 (2H, m), 7.42 (2H, m), 8.07 (1 H, d, J = 2.6 Hz), 8.11 (1 H, d, J = 2.6 Hz).

[Example 30] 3-(5-(4-(Pyridin-2-yloxymethyl)-benzyl)-isoxazol-3-yl)-pyridin-2-ylamine

[0505]

- 10 [6069] To a solution of 5-chioro-3-[6-4-(pyridin-2-y/osymethyl-benzyl-)-soxazoi-3-yl-)-pyridin-2-ylamine (37 mg. 94 μm0) described in Manufacturing Example 30-1-3 in N methyl 2-pyrolidinone (2 mL) were added formic acid (5.3 μL, 0.14 mmol), NI-discopropylethylamine (49 μL, 0.28 mmol) and bist(tri-lerf-butylphosphine)palladum (0) (3.6 mg.) 19 μm0) at room temperature, which was stirred under nitrogen atmosphere for 1 hour and 25 minutes at 100°C. Water and ethyl acetta were added to the reaction solution at room temperature, which was then filtered through a Celle pact of the filtered through the Celle pact of the filtered through a Celle pact of the filtered through a Celle pact of the filtered through a Celle pact of the filtered through the Celle pact of the filtered through the Celle pack of the filtered through the Celle pack of the Ce
- 20 ¹H-NMR Spectrum (CDCl₃) 8 (ppm): 4.14 (2H, s), 5.39 (2H, s), 6.27 (1 H, s), 6.49 (2H, brs), 6.69 (1 H, dd, J = 4.9, 7.5 Hz), 6.81 (1 H, d, J = 8.4 Hz), 6.88-6.91 (1 H, m), 7.31 (2H, d, J = 8.0 Hz), 7.47 (2H, d, J = 8.0 Hz), 7.57-7.62 (1 H, m), 7.68 (1 H, dd, J = 1.8, 7.5 Hz), 8.09 (1 H, dd, J = 1.8, 4.9 Hz), 8.17-8.19 (1 H, m).
 MS m(=(SS) 358.11 (MH)
- The starting material, 5-chloro-3-(5-(4-(pyridin-2-yloxymethyl)-benzyl)-isoxazol-3-yl)-pyridin-2-ylamine, was synthesized as follows.

[Manufacturing Example 30-1-1] 2-(4-Chloromethyl-benzyloxy)-pyridine

[0507]

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- 40 [0508] A mixture of (4-[pyridin-2-yioxymethyl)-phenyl)methanol (540 mg, 2.51 mmol) described in Manufacturing Example 2-1-1, triphenylphosphine (856 mg, 3.27 mmol) and carbon letrachloride (10.8 g, 10.2 mmol) was stirred under reflux for 2 hours and 10 minutes. The reaction solution was cooled to room temperature, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: a ceitic acid = 8:1) to obtain the title compound (300 mg, 51.1 %).
- 45 1H-NMR Spectrum (DMSO-d₆) δ (ppm): 4.76 (2H, s), 5.35 (2H, s), 6.86-6.90 (1 H, m), 6.97-7.20 (1 H, m), 7.44 (4H, s), 7.70-7.76 (1 H, m), 8.15-8.18 (1H m).

[Manufacturing Example 30-1-2] 2-(4-Prop-2-ynyl-benzyloxy)-pyridine

50 [0509]

[0510] To a solution of trimethylsbig acetylene (496 µ.1, 5.51 mmol) in tetrahydroturan (15 m.l.) was added ethyl magnesium bromide (3 M diethyl ether solution, 1,09 m.l., 3.28 mmol) under nitrogen atmosphere at room temperature, which was stiered for 30 minutes at 65°C. The reaction solution was cooled to room temperature, and copper (1) bromide (168 mg, 1.17 mmol) and 2/4-chloromethyl-benzyloxy)-pyridine (548 mg, 2.34 mmol) manufactured in Manufacturid in

1H-NMR Spectrum (DMSO-d_e) δ (ppm): 3.04 (1 H, m), 3.61 (2H, d, J = 2.6 Hz), 5.30 (2H, s), 6.83-6.87 (1 H, m), 6.95-6.99 (1 H, m), 7.30-7.32 (2H, s), 7.36-7.40 (2H, m), 7.68-7.73 (1 H, m), 8.14-8.16 (1 H, m).

[Manufacturing Example 30-1-3] 5-Chloro-3-(5-(4-(pyridin-2-yloxymethyl)-benzyl)-isoxazol-3-yl)-pyridin-2-ylamine

[0511]

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[0512] To a solution of 2-amino-5-chloro-N-hydroxypridine-3-carboxyimidoy chloride (50 mg, 242 µmo) described in Manufacturing Example 29-1-c in ternhydrofuran 6 ml.) were added trietlynamine (14 µL 282 µmo) add 2(4-prop-2-ynyl-benzyloxy)-syridine (271 mg, 243 µmol, purity: 20%) described in Manufacturing Example 30-1-2 at room temperature, which was attired for 30 minuthes at room temperature, and further stirred under reflux for 2 hours and 25 minutes. The reaction solution was cooled to room temperature, and concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 5: 1) to obtain the title compound (37 mg, 39%).

¹H-NMR Spectrum (DMSO-d₄) δ (ppm): 4.22 (2H, s), 5.34 (2H, s), 6.86 (1 H, d, J = 8.2 Hz), 6.97-7.01 (1 H, m), 7.04 (1 H, s), 7.07 (2H, brs), 7.34 (2H, d, J = 8.0 Hz), 7.44 (2H, d, J = 8.0 Hz), 7.70-7.74 (1 H, m), 8.09 (1 H, d, J = 2.6 Hz), 8.14 (1 H, d, J = 2.6 Hz), 8.16 8.14 (1 H, m).

[Example 31] 3-(1 -(4-Benzyloxy-benzyl)-1H-pyrazol-4-yl)-pyridin-2-ylamine

[0513]

[0514] To a solution of 2 amino-3-bromosyridine (44.1 mg, 0.26 mmol) in anhydrous tetrahydrofuran (7 mL) were added 1-4-6-bracyloxy-bezpy)-4-bribuylstannay+1-bryanzae (141 mg, 0.26 mmol) serobed in Manufacturing Example 31-1-2, copper (f) lodde (19.4 mg, 0.10 mmol) and bis(triphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylphenylpheny

The starting material, 1-(4-benzyloxy-benzyl)-4-tributylstannanyl-1H-pyrazole, was synthesized as follows.

[Manufacturing Method 31-1-1] 1-(4-Benzyloxy-benzyl)-4-bromo-1H-pyrazole

[0515]

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- Sign [516] To a solution of 2-bromopy/azole (\$00 mg, 3.40 mmol) in NN-dimethylformamide (10 mL) was added sodium hydride (19 mg, 4.08 mmol, 50% in oil) on an ice bath (10°C) under nitrogen atmosphere, which was stirred for 30 minutes at room temperature. 4-Benzyloxybenzyl chloride (791 mg, 3.40 mmol) was then added and stirred for 60 minutes at room temperature. The rescition inxiture was partitioned into water and thily scetable at room temperature. The organic layer was washed with water and eathrated aquoues sodium chloride, and dired over anthyrous magnesium 49 sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl scatchs: heptane = 1.5 to obtain the title compound (1.1 g, 94%). 1H-NMR Spectrum (DMSO-dg.) & (pm): 5.04 (2H, s), 5.17 (2H, s), 6.94 (2H, d, J = 8.8 Hz), 7.17 (2H, d, J = 8.8 Hz), 7.31 (1 H, s), 7.39-74 (1 H, m), 7.47 (1 H, m), 7.47 (1 H, m), 7.47 (1 H, m).
- 45 [Manufacturing Example 31-1-2] 1-(4-Benzyloxy-benzyl)-4-tributylstannanyl-1H-pyrazole

[0517]

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[0518] To a solution of 1-(4-benzyloxy-benzyl)-4-bromo-1*H*-pyrazole (1.10 g, 3.20 mmol) described in Manufacturing Example 31-1-1 in xylene (20 mL) were added tetrakis(triphenylphosphine)palladium (0) (370 mg, 0.32 mmol) and hexa-

n-buly i stannane (5.57 g, 9.00 mmol) under nitrogen atmosphere, which was stirred for 2 hours at 140°C. Water and ethy acetate were added to the reaction indiure at room temperature, which was then filtered through a Celle pad, and the filtrate was partitioned into water and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anti-yidrous magnatesium sulfate, and the solvent was everyoned under areducely pressure. The residue was purified by silica gel column chromatography (ethyl acetate : heptane = 1 : 5) to obtain the little compound (141 mm 8%).

¹H-NMR Spectrum (CDCl₂) δ (ppm): 0.87 (9H, t, J = 7.2 Hz), 0.92-1.00 (6H, m), 1.26-1.35 (6H, m), 1.46-1.54 (6H, m), 5.05 (2H, s), 5.27 (2H, s), 6.93-6.95 (2H, m), 7.14-7.17 (2H, m), 7.23 (1H, s), 7.31-7.43 (5H, m), 7.46 (1H, s).

Example 32|3-(1-(4-(Pyridin-2-vloxymethyl)-benzyl)-1H-pyrazol-4-yl)-pyridin-2-ylamine

[0519]

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NH₂

[0520] To a solution of 34 (*Heyrazol-4-y*)-pyridin-2-ylamine (150 mg, 0.94 mmol) described in Manufacturing Example 32-1-4 in N,N-dimethylformamide (10 mL) was added sodium hydride (48.7 mg, 1.22 mmol, 60% in oil) on an ice bath (0°C) under nitrogen atmosphere. Following 40 minutes of stirring at room temperature. 2-46-chloromethyl-benzyloxyl-pyriddine (228 mg, 0.98 mmol) described in Manufacturing Example 30-1-1 was added and stirred for 30 minutes at room temperature. The reaction mixture was partitioned into water and eithyl acetalt at room emperature. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetalts ethoration 2, 25%).

 $\begin{array}{lll} \text{H-MMR Spectrum (DMSO-dq)} \delta \left(\text{pprij}: 5.33 \, (\text{H. s}), 5.53 \, (\text{H. h}), 8,540 \, (\text{H. hr}), 8.64 \, (\text{H. d}), 4.64, 7.44 \, (\text{H. d}), 5.46, 7.44 \, (\text{H. d}), 7.34 \, (\text{H. hr}), 7.86 \, (\text{H. d}), 7.42 \, (\text{H. h. y.}), 8.64 \, (\text{H. d}), 7.42 \, (\text{H. h. y.}), 8.44 \, (\text{H. d}), 7.42 \, (\text{H. h. y.}), 8.44 \, (\text{H. d}), 7.42 \, (\text{H. h. y.}), 8.15 \, (\text{H. h. d}), 7.24 \, (\text{H. h. y.}), 8.15 \, (\text{H. h. d}), 7.66 \, (\text{H. h. d.}), 7.66 \, (\text{H. h. d. h. d.}), 7.66 \, (\text{H. h. d. h. d.}), 7.66 \, (\text{H. h. d.}), 7.66 \, (\text{H. h. d. h. d.}), 7.66 \, (\text{H. h. d. h. d.}), 7.66$

The starting material, 3-(1H-pyrazol-4-yl)-pyridin-2-ylamine, was synthesized as follows.

[Manufacturing Example 32-1-1] 4-Bromo-1-trityl-1H-pyrazole

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[0822] To a solution of 4-bromopyrazole (10.0 g. 68.0 mmol) in N.N-dimethylformamide (100 mL) was added dropwise triethylamine (23.7 mL, 170 mmol) under nitrogen atmosphere at room temperature. Trity chloride (37.9 g. 136 mmol) was added to the reaction solution on an ice bath (0°C), and stirred for 3 hours at 70°C. Water (400 mL) was added to the reaction solution to precipitate the solids. The precipitated solids were filtered and dried under a reduced pressure. The solids were then azeotropically dried with toluene to obtain the title compound (2.9 g. 87%). "H-NMR Spectrum (DMSC-d₀) & (pcm)r, 70.4-7.07 (61, m), 7.35-7.38 (91, m), 7.52 (114, d. J = 0.4 Hz), 7.76 (114, d. J = 0.8 Hz).

[Manufacturing Example 32-1-2] 4-(4,4,5,5-Tetramethyl-(1,3,2)dioxaborolan-2-yl)-1-trityl-1 H-pyrazole

[0523]

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O-B

[0524] A mixture of 4-bromo-4-trilly-11-brynzole (4.8.g. 12.2 mmol) described in Manufacturing Example 32-1-1, bis (pinacolate)diboran (5.0 g. 19.7 mmol), potassium acetate (3.82 g. 3.6.9 mmol.), 1;1 bis (pinenylphosphino)lerocene dichloropalatolum (III) (450 mg. 0.62 mmol) and dimethyl sulfoxide (50 ml.) was stirred under argon atmosphere for 17 hours and 10 minutes at 80°C. The reaction solution was allowed to room temperature, and partitioned into water and eithy acetate. The organic layer was concentrated under a reduced pressure. The reaction was purified by eitha gel chromatography (heptane: ethyl acetate = 4:1), Heptane was added to the solids obtained by concentrating the eluate under a reduced pressure, which were then irradiated by ultrasonic wave and filtered to obtain the title compound (1.51 g. 28.0%).

¹H-NMR Spectrum (CDCl₂) δ (ppm): 1.30 (12H, s), 7.10-7.16 (6H, m), 7.26-7.31 (9H, m), 7.75 (1 H, s), 7.94 (1 H, s).

[Manufacturing Example 32-1-3] 3-(1-Trityl-1H-pyrazol-4-yl)-pyridin-2-ylamine

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[0526] 4-(4,4,5,5-Tetranethyl-(1,3,2)dioxabrotan-2-yl)-1-trily-1H-pyrazole (3,2 g, 7.33 mmo) described in Manufacturing Example 32-1-2, 3-bromo-pyridine-2-ylamine (1,14 g, 6.60 mmo), tetrakis (triphenylphosphine)palladum (0) (42mg, 0.37 mmo), toluene (40 mL), 2 M aqueous sodium carbonate solution (10 mL) and ethanol (20 mL) were stirred for 1 hour at 95°C. The reaction solution was allowed to room temperature, and partitioned into water and ethyl acetate. The ethyl acetate layer was washed with water once, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel chromatography (heptane: ethyl acetate = 1/2) to obtain the title compound (2.3 g, 78.0%). 1 H-NMR Spectrum (DMSO-d₆) δ (ppm): 5.52 (2H, brs), 6.57 (1H, dd, J = 7.2, 4.8 Hz), 7.10-7.16 (6H, m), 7.28-7.38 (9H, m), 7.42 (1 H, d, J = 7.2 Hz), 7.66 (1H, s), 7.84 (1 H, d, J = 4.8 Hz), 7.92 (1 H, s).

[Manufacturing Example 32-1-4] 3-(1H-Pyrazol-4-vl)-pyridin-2-vlamine

[0527]

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N NH

(20) [0.528] 3-(1-Trilyi-1 H-pyrazol-4-yl)-pyrdin-2-ylamine (2.3 g, 5.71 mmg) described in Manufacturing Example 32-1-3, 2 N hydrochloric acid (15 mL), methanol (15 mL) and tetrahydrofuran (10 mL) were stirred for 30 minutes at 70°C. The reaction solution was allowed to room temperature, and partitioned into water and ethyl acetate. Saturated softum bicarbonate solution was added to the separated aqueous layer, which was then extracted with ethyl acetate 6 times. The ethyl acetate is given were combined and the solvent was exporated under a enduced pressure. The residue was 55 purified by silica gel chromatography (ethyl acetate, then ethyl acetate: methanol = 10 : 1) to obtain the title compound (855 m. 68.3%).

¹H-NMR Spectrum (DMSO-d_s) δ (ppm): 5.59 (2H, brs), 6.62 (1H, dd, J = 4.8, 7.6 Hz), 7.49 (1 H, d, J = 7.2 Hz), 7.88 (1 H, d, J = 4.8 Hz), 7.72-8.15 (2H, brs), 12.9 (1 H, brs).

[Example 33] 3-(1-(4-Butoxymethyl-benzyl)-1H-pyrazol-4-yl)-pyridin-2-ylamine

[0529]

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8.1 Hz), 7.39 (1 H, dd, J = 1.8, 7.3 Hz), 7.58 (1 H, s), 7.73 (1 H, d, J = 0.7 Hz), 8.00 (1H, dd, J = 1.8, 5.1 Hz). The starting material, 1-butoxymethyl-4-chloromethyl-benzene, was synthesized as follows.

[Manufacturing Example 33-1-1] 4-Butoxymethyl-benzonitrile

[0531]

[0532] To a mixture of sodium hydride [270 mg, 11 mmol, 68% in oil) and tetrahydrofuran [20 mL) was added r-butand (1.1 mL, 12 mmol) at 0°C, which was stirred for 45 minutes at room temperature. The reaction mixture was cooled to 0°C, and a mixture of 4-cyanobenzyl bromble (1.5 g, 7.4 mmol) and tetrahydrofuran (10 mL) was added dropwise at that temperature. The reaction mixture was stirred for 3 hours at room temperature, and NN-dimethylformamide (10 mL) was added to the reaction mixture was stirred for 3 hours at room temperature, and NN-dimethylformamide (10 mL) was added to the reaction mixture was partitioned into water and diethyl ether. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatoraby (18 mL) addets 1- betalane a 1.5 th obtain the title compound (12 o. 84%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 0.93 (3H, t, J = 7.3 Hz), 1.37-1.46 (2H, m), 1.59-1.66 (2H, m), 3.50 (2H, t, J = 6.6 Hz), 4.55 (2H, s), 7.43-7.46 (2H, m), 7.62-7.65 (2H, m).

[Manufacturing Example 33-1-2] 4-Butoxymethyl-benzylamine

20 [0533]

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[0534] To a mixture of lithium aluminum hydride (600 mg, 13 mmol, purtly, 80%) and tetrahydrofuran (10 mL) was added a mixture of 4-butoxymetry-benzonitale (600 mg, 22 mmol) described in Manufacturing Example 33-1-1 and tetrahydrofuran (10 mL) at 0°C, which was stirred for 4 hours at room temperature. 28% Aqueous ammonia solution was added dropwise to the reaction mixture as was warmed to come temperature and filtered. The filtrate was concentrated under a reduced preserve to obtain the title compound (620 mg, 101 %) as a crude product. 11-h-MMR Spectrum (CDCl₂) 8 (ppm; 0.92 (81t, t.) = 7.3 Hz), 1.37-1.44 (2H, m), 1.56-1.63 (2H, m), 3.47 (2H, t.,) = 6.8 Hz), 3.86 (2H, 3.49 (2H, t.), 27.77-32 (4H, m).

[Manufacturing Example 33-1-3] (4-Butoxymethyl-phenyl)-methanol

[0535]

[0536] To a mixture of 4-butoxymethyl-benzylamine (250 mg, 1.3 mmol) described in Manufacturing Example 33-1-2, acetic acid (2 ml.) and water (2 ml.) was added sodium nitrite (1.1 g, 16 mmol) a 0°C, which was stirred for 40 minutes at room temperature. The reaction mixture was prelimed into eith via scalate and water. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. Methanol (2 ml.) and potassium carbonate (360 mg, 2.6 mmol) were added to the residue, and the reaction mixture was stirred for 1.5 hours at room temperature. The reaction mixture was concentrated under a reduced pressure. The residue was purified by neutral silica gel column chromatography (etnyl acetale: heptane = 1: 1) to obtain the title compount (200 mg, 78%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 0.92 (3H, t, J = 7.3 Hz), 1.35-1.44 (2H, m), 1.57-1.64 (2H, m), 3.47 (2H, t, J = 6.6 Hz), 4.50 (2H, s), 4.69 (2H, s), 7.34 (4H, s).

[Manufacturing Example 33-1-4] 1-Butoxymethyl-4-chloromethyl-benzene

[0537]

[0539] A mixture of (4-butoxymethyl-phenly)-methanol (190 mg, 0.98 mmol) described in Manufacturing Example 33-1-3, hiphenphopsphile (310 mg), 1.2 mmol) and cabnot herathoridod (3 ml.) was sittered under reflux for Phours. The reaction mixture was cooled to room temperature, and concentrated under are reduced pressure. The residue was purified by reutral sizing ed column-chromatography (ethyl scate te: heptane = 1.15) to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain the filter compound (190 mg, 86%), 11-150 to obtain th

[Example 34] 3-(1-(4-Phenoxy-benzyl)-1 H-pyrazol-4-yl)-pyridin-2-ylamine

[0539]

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[0540] To a solution of 3-{1/H-ynyacol-4-yl-pyridin-2-ylamine (20 mg, 0.13 mmol) described in Marufacturing Example 32-1-4 in NN-4/methylformamice (10 mt), was added sodium hybride (7.5 mg, 0.15 mmol, 60% in 0l) under nitrogen atmosphere on an ice bath (0°C), which was stirred for 30 minutes at room temperature. 1-Chloromethyl-4-phenoxy-berezene (32.8 mg, 0.15 mmol) described in Manufacturing Example 34-1-1 was then added to the mixture and stirred for 30 minutes at room temperature. The reaction mixture was partitioned into water and ethyl acetate at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was exported under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 2:1, then ethyl acetate only) to obtain the title compound (41 mg, 86%, purity.

¹H-NMR Spectrum (DMSO-d₆) 6 (ppm): 5.33 (2H, s), 5.60 (2H, brs), 6.61 (1 H, dd, J = 4.8, 7.4 Hz), 6.98-7.01 (2H, m), 7.12-7.16 (1 H, m), 7.34-7.40 (2H, m), 7.49-7.65 (5H, m), 7.77 (1 H, s), 7.77 (1 H, dd, J = 1.2, 5.0 Hz), 8.18 (1 H, s). The starting material, 1-chloromethyl-4-phenoxy-benzene, was printesized as follows.

[Manufacturing Example 34-1-1] 1-Chloromethyl-4-phenoxy-benzene

[0541]

[0542] To a solution of (4-phenoxy-phenyl)-methanol (408 mg, 2.04 mmol) in carbon tetrachioride (8.2 mL) was added triphenylphosphine (642 mg, 2.45 mmol) under nitrogen atmosphere at room temperature, and the reaction solution was stirred under reflux for 7 hours and 40 minutes. The reaction mixture was cooled to room temperature and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl acetate = 10: 1) to obtain the site compound (409 mg, 92%).

1H-NMR Spectrum (DMSO-d_e) δ (ppm): 4.76 (2H, s), 6.98-7.05 (4H, m), 7.15-7.19 (1 H, m), 7.39-7.46 (4H, m),

[Example 35]3-(1-(3-Phenoxy-benzyl)-1H-pyrazol-4-yl)-pyridin-2-ylamine

[0543]

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N NH

15 (0544) To a solution of 3-(1H-pyrazol-4-yl)-pyridin-2-ylamine (20 mg, 0.1 mmol) described in Manufacturing Example 32-1-4 in N,N-dimethylformamide (10 mL) was added sodium hydride (7.5 mg, 0.19 mmol, 60% in oil) under nitrogen atmosphere on an ice bath (70°C), which was stirred for 40 minutes at room temperature. T-chiroromethyl-3-phenory-benzene (32.8 mg, 0.15 mmol) described in Manufacturing Example 35-1-1 was then added and stirred for 30 minutes at room temperature. The registic personal results are dent byla declate at room temperature. The organic 20 layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by 14H slicic gel column chromatography (drifty) acetate: enlyb ril acetate enlyb to obtain the title compound (20 mg, 47%).

¹H-NMR Spectrum (DMSO-d₂) δ (ppm): 5.35 (2H, s), 5.59 (2H, brs), 6.62 (1 H, dd, J = 1.2, 7.4 Hz), 6.90-6.95 (2H, m), 6.99-7.06 (3H, m), 7.13-7.17 (1 H, m), 7.34-7.41 (3H, m), 7.48 (1 H, dd, J = 2.0, 7.4 Hz), 7.70 (1 H, d, J = 0.8 Hz), 7.87 (1 H, dd, J = 2.0, 5.6 Hz), 8.16 (1 H, dJ = 0.8 Hz).

The starting material, 1-chloromethyl-3-phenoxy-benzene, was synthesized as follows.

[Manufacturing Example 35-1-1] 1-Chloromethyl-3-phenoxy-benzene

Ø [0545]

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[0546] To a solution of (3-phenoxy-phenyl)-methanol (2.00 g, 10.0 mmol) in carbon tetrachloride (40 mL) was added triphenylphosphine (3.15g, 12.0 mmol) at room temperature. The reaction solution was stirred under nitrogen ent mosphere for 5 hours and 40 minutes under reflux. The reaction mixture was cooled to room temperature and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl acetate = 10:1) to obtain the title compound (2.05 g, 94%).

¹H-NMR Spectrum (DMSO-d_p) δ (ppm): 4.37 (2H, s), 6.94-6.97 (1 H, m), 7.00-7.03 (2H, m), 7.05-7.06 (1 H, m), 7.13-7.20 (3H, m), 7.37-7.41 (2H, m).

[Example 36]3-(1-(4-Benzyloxy-benzyl)-1H-pyrazol-4-yl)-pyridin-2,6-diamine

[0547]

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[0548] To a solution of 3 (1H pyrazol 4-yf) pyridin 2,6-diamine (25 mg, 0.14 mmol) described in Manufacturing Example 36-12 in N.N-dimethyldomamide (10 mL) was added sodium hydriae (8.6 mg, 0.22 mmol, 60% in oil) under introgen atmosphere on an ice bald h(°C), which was stirred for 30 minutes at room temperature. 4-Benaryloxybenzyl chloride (49.8 mg, 0.22 mmol) was then added and stirred for 30 minutes at room temperature. The reaction mixture was partitioned into water and ethyl scetate at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium suitate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl scetate : heptane =2:1, then ethyl scetate or in the oblast intertion group und (24 mc, 45%).

¹H-NMR Spectrum (DMSO-d_b) δ (ppm): 5.06 (2H, brs), 5.09 (2H, s), 5.21 (2H, s), 5.43 (2H, brs), 5.77 (1 H, d, J = 8.0 Hz), 6.977.00 (2H, m), 7.15 (1 H, d, J = 8.0 Hz), 7.23-7.28 (2H, m), 7.30-7.34 (1 H, m), 7.36-7.44 (4H, m), 7.56 (1 H, d, J = 1.2 Hz).

The starting material, 3-(1H-pyrazol-4-vl)-pyridin-2.6-diamine, was synthesized as follows.

[Manufacturing Example 36-1-1] 3-(1 Trityl-1 H-pyrazol-4-yl)-pyridin-2,6-diamine

[0549]

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[0550] To a solution of 3-lodo-pyridin-2, 6-diamnine (3.3 g. 7.74 mmol, purity. 70%) described in Manufacturing Exemple 13-1-1 in totalen (60 mL), were added ethannol (26 mL). 2 N aqueous sodium carbonate solution (12 5 mL), 4-44,6.56-tetramethyi-(1,3,2)dioxaborolan-2-yi)-1-trily-1-1-y-pyrazole (3.3 g. 7.56 mmol) described in Manufacturing Example 32-1-2 and tetraksitriphenry/shosphine)palisidium (0) (1.02 g. 0.88 mmol) under nitrogen atmosphere, which was streed for 2.5 and tetraksitriphenry/shosphine)palisidium (0) (1.02 g. 0.88 mmol) under nitrogen atmosphere, which was streed for 2.5 and tetraksitriphenry/shosphine)palisidium (0) (1.02 g. 0.88 mmol) under nitrogen atmosphere, which was streed for 2.5 and 5 ml of 2.61 ml of

¹H-NMR Spectrum (CDCl₃) δ (ppm): 4.63 (2H, brs), 4.79 (2H, brs), 5.90 (1 H, d, J = 8.0 Hz), 7.16-7.20 (6H, m), 7.29-7.32 (10H, m), 7.45 (1H, s), 7.77 (1 H, s).

[Manufacturing Example 36-1-2] 3-(1H-pyrazol-4-yl)-pyridin-2,6-diamine

5 [0551]

[0552] To a solution of 3-(1-trity-IH-pyrazol-4-yf)-pyrdin-2.6-diamine (10.0, 2.6.7 mmol) described in Manufacturing Example 36-1-1 in methylene chloride (14 mL) was added trifluoroacetic acid (7 mL) under nitrogen atmosphere, which was stirred for 1 hour at room temperature. The reaction mixture was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate, then ethyl acetate: methanol = 10:1) to obtain the title compount (600 mc, 60%).

¹H-NMR Spectrum (DMSO- d_0) δ (ppm): 5.04 (2H, brs), 5.41 (2H, brs), 5.78 (1 H, d, J = 8.4 Hz), 7.16 (1 H, d, J = 8.0 Hz), 7.62 (1 H, brs), 7.78 (1 H, brs), 12.8 (1 H, brs).

[Example 37] 3-(1-(4-(Pyridin-2-yloxymethyl)-benzyl)-1 H-pyrazol-4-yl)-pyridin-2.6-diamine

[0553]

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[0554] To a solution of 3-(1 H-pyrazol-4yl)-pyrdin-2,6-diamine (25 mg, 0.14 mmol) described in Manufacturing Example 38-1-2 in N,N-dimethylformanide (3 mL) was added sodium hydride (8.6 mg, 0.22 mmol, 60% in oil) under nitrogen atmosphere on an ice bath (0°C). Following 30 minutes of stirring at room temperature, 2-(4-chloromethyl-benzyloxy)-pyrdine (43.4 mg, 0.19 mmol) described in Manufacturing Example 30-1-1 was added and stirred for 30 minutes at 60°C. The reaction mixture was partitioned into water and ethyl acatelate at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl scetate: heptane 2-1, then ethyl acatelate only) to obtain the title compound (22 m mg, 43%).

14-NMR Spectrum (DMSC-d_b) 8 (pm): 5.07 (2H, brs), 5.30 (2H, s), 5.32 (2H, s), 5.43 (2H, brs), 5.76 (1 H, d, J = 8.0 Hz), 7.86 (1 H, m), 6.96-7.00 (1 H, m), 7.16 (1 H, d, J = 8.0 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.41 (2H, d, J = 7.6 Hz), 7.58 (1H, s), 7.69-7.73 (1 H, m), 7.94 (1 H, s), 8.15-8.17 (1H, m).

[Example 38] 3-(1-(4-Butoxymethyl-benzyl)-1H-pyrazol-4-yl)-pyridin-2,6-diamine

5 [0555]

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[0556] To a solution of 3-(1H-pyrazot-4-y)-pyridin-2,6-diamine (20 mg, 0.11 mmol) described in Manufacturing Example 36-1-2 in N,N-dimethylformamide (4 ml.) was added sodium hydride (5.9 mg, 0.15 mmol, 60% in oil) under nitrogen atmosphere on an ice bath (0°C) Following 30 minutes of stirring at room temperature, 1-butoxymethyl-4-chloromethyl

benzene (28.7 mg, 0.13 mmol) described in Manufacturing Example 33-1.4 was added and stirred for 30 minutes at own temperature. The reaction mixture was partitioned into water and ethyl acetate at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride, and dired over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silicia gel column chromatograph (eth) excetate : he plane = 21, 1, then ethyl excetate) to botain the title compound (28.0 mg, 72%).

14-hMR Spectrum (DMSO-d₂) δ (ppm); 0.864 (3H, d, J = 7.6 Hz), 1.30-1.35 (2H, m), 1.47-1.54 (2H, m), 3.40 (2H, d, J = 6.4 Hz), 4.42 (2H, s), 5.07 (2H, brs), 5.29 (2H, s), 5.43 (2H, brs), 5.78 (1 H, d, J = 8.4 Hz), 7.16 (1 H, t, J = 8.0 Hz), 7.24-7.29 (4H, m), 7.58 (1 H, s), 7.93 (1 H, s).

Example 39] 3-(4-(4-Benzyloxy-benzyl)-pyrazol-1-yl)-pyridin-2-ylamine

[0557]

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[0558] To a mixture of 3-(4-brom-cyvazot-1-yl)-pyridin-2-ylamine (34 mg, 0.14 mmol) described in Manufacturing Example 39-2-1. As many data-2-1. As many dat

MS m/e (ESI) 357.18 (MH+)

The starting material, 3-(4-bromo-pyrazol-1-yl)-pyridin-2-ylamine, was synthesized as follows.

35 [Manufacturing Example 39-1-1] 2,2-Dimethyl-N-pyridin-2-yl-propionamide

[0559]

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(0560) To a solution of 2-minopyridine (60.0 g, 831 mmo) in methylene chloride (600 mL) were added triethylamine (61.1 mL, 984 mmo) and pivaloy chloride (7.1 mL, 984 mmo) at 0°C, which was stirted for 4 hours and 90 minutes at room temperature. The reaction solution was partitioned into vater and methylene chloride. The organic layer was washed with vater and saturated aqueous sodium chloride, and office over anhylrone magnesium suitate, and the solvent was evaporated under a reduced pressure. To a solution of the resulting residue in methantol (300 mL) was added potassium carbonate (7.3 4, 9.51 mmo) at 0°C, which was stirred for 90 minutes at room temperature. The reaction solution was partitioned into vater and ethyl secteta at room temperature. The organic layer was washed with asturated aqueous codium chlorided and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. Heptane (300 mL) was added to the residue, and the precipitated solidis were filtrared to obtain the title compound (80.2 g, 85%). The filtrate was then concentrated under a reduced pressure, and he residue was pullfield by sisting set counter chromostography (heptane-ethyl sectetae = 2.1) to obtain the title compound (12.2 g, 15%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.22 (9H, s), 7.06-7.09 (1 H, m), 7.72-7.77 (1 H, m), 8.01-8.03 (1 H, m), 8.29-8.31

(1 H, m), 9.71 (1 H, s).

[Manufacturing Example 39-1-2] N-(3-lodo-pyridin-2-yl)-2,2-dimethyl-propionamide

[0561]

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[0582] To a mixture of 2.2-dimethyl-N-pyridin-2-y-propionamide (3.0 g, 1.7 mmol) described in Manulacturing Example 39-1-1, N.N.W.N'-teramethylethylenediamine (8.3 mL, 42 mmol) and tetrahydrofuran (60 mL) was acided dropwise n-butyl lithium (1.6 M n-hexane solution, 30 mL, 47 mmol) at -78°C, which was stirred overnight at 0°C. Iodine (8.8 g, 27 mmol) was acided to the reaction mixture at -78°C, and stirred for 1.5 hours at 0°C. Water and saturated aqueous sodium incisualfase solution were added to the reaction mixture, which was then extracted with explaceta. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : heptane = 2 : 1) to obtain the title compound (2.9 g, 57%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.38 (9H, s), 6.85 (1H, dd, J = 4.8, 7.9 Hz), 7.94 (1 H, brs), 8.11 (1 H, dd, J = 1.7, 7.9 Hz), 8.46 (1 H, dd, J = 1.7, 4.6 Hz).

[Manufacturing Example 39-1-3] N-(3-(4-Bromo-pyrazol-1-yl)-pyridin-2-yl)-2,2-dimethyl-propionamide

[0563]

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[0564] To a mixture of N-(3-lodo-pyridin-2-yl)-2,2-dimethyl-propionamide (380 mg, 1.2 mmol) described in Manufacturing Example 39-1-2 and folluene (10 mL) were added 4-bromopyrazole (160 mg, 1.1 mmol), opper (1) lodde (11 mg, 0.056 mmol), frans-1,2-cyclohexacediamine (26 mg, 0.22 mmol) and potassium carbonate (340 mg, 2.5 mmol) at room temperature, which was stirred overnight at 110°C. The reaction mixture was concentrated under a reduced pressure. The stickle was purified by NH silica gel column chromatography (ethyl scatate: heptane = 2:1) to obtain the title compound (190 mg, 52%).

 1 H-NMR Spectrum (DMSO- 2 0- 3 0 (ppm): 1.10 (9H, s), 7.45 (1 H, dd, J = 4.8, 8.1 Hz), 7.84 (1H, s), 8.00 (1 H, dd, J = 1.7, 7.9 Hz), 8.23 (1 H, s), 8.47 (1 H, dd, J = 1.7, 4.8 Hz), 9.83 (1H, brs).

[Manufacturing Example 39-1-4] 3-(4-Bromo-pyrazol-1-yl)-pyridin-2-ylamine

[0565]

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[0866] A mixture of Nt-(4-thromo-pyrazol-1-y)-pyridin-2-y)-2-dimethylpropionamide (380 mg, 12 mmol) described in Manufacturing Example 39-1-3 and aqueous 2.6 N hydrochloric acids oslution (2.1 M) was sirred overnight at 105°C. The reaction mixture was cooled to 0°C, and 6 N sodium hydroxide solution (1 ml.) was added. The resulting solids were filtered to obtain the title compound (100 mg, 278-), H-NMR Spectrum (DMS-O_{4.6}) 6,690; 6.34 (24, h.) 8, 6.89 (1 H, dd, $_2$ + 8, 7.7 H-), 7.62 (1 H, dd, $_3$ = 1.7, 7.7 H-2), 7.90 (1 H, s), 8.02 (1 H, dd, $_3$ = 1.7, 4.8 Hz), 8.45 (1H, s). The statring material (4-beyravovb-percyl-through-stangen, was seminosized as follows:

[Manufacturing Example 39-2-1] (4-Benzyloxy-benzyl)-tributyl-stannane

[0567]

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[0568] To a mixture of disopropylamine (1.1 ml., 7.7 mmol) and tetrahydrofuran (20 ml.) was added dropwise n-buyll filthim (1.6 M n-hexane solution, 4.5 ml., 7.1 mmol) a 1-78°C, which was stirred for 30 minutes at the temperature. Tributyltin hydride (1.7 ml., 6.5 mmol) was added dropwise to the reaction mixture at the same temperature and then stirred for 30 minutes at 0°C. The reaction mixture was cooled to -78°C, and a mixture of 4-benzyloxybenzyl chloride (1.5 g. 6.5 mmol) and tetrahydrotran (10 ml.) was added dropwise at that temperature. The reaction mixture was pradually warmed to room temperature. The reaction mixture was partitioned into water and n-heptane. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by neutral silica gel column diromatography (ethyl acetate: heptane = 1: 30 to obtain the title compound (2.8 g. 83%).

2.24.(2H, s), 5.01 (2H, s), 6.80-6.83 (2H, m), 6.88-6.91 (2H, m), 7.29-7.44 (5H, m).

[Example 40] 3-(3-(6-Phenoxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[0569]

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[0570] To a solution of (2-phenoxy-pyridin-5-yi)-acetohydroximoyl chloride (63 1 mg, 225 µm0) described in Manufacturing Example 40-14 and 3-ethynyl-pyridin-26-diamine (20.0 mg, 150) µm0) obscribed in Manufacturing Example 31-13 in tetrahydrofuran (1.3 mf.) was added trietlynimine (41.8 µL, 300 µm0) at room temperature, which was stirred for 65 minutes at 50°C. The reaction solution was allowed to room temperature and partitioned into water and ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous angenesium sullate and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by

NH silica gel column chromatography (ethyl acetate: methanol = 10:1) to obtain the title compound (52 mg, 97%). 1H-NMR Spectrum (DMSO-dg) & (5ppm): 938 (2H, s), 5.79 (2H, s), 6.81 (1H, d, J = 8.4 Hz), 6.10 (2H, s), 6.40 (1 H, s), 6.97 (1 H, d, J = 8.4 Hz), 7.08-7.10 (2H, m), 7.16-7.20 (1H, m), 7.37-7.41 (2H, m), 7.50 (1H, d, J = 8.4 Hz), 7.76 (1 H, dd) = 22.8 (4 Hz), 8.11 (1 H, d) = 2.4 Hz).

The starting material, (2-phenoxy-pyridin-5-yl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 40-1-115-Bromo-2-phenoxy-pyridine

[0571]

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[0572] To a solution of phenol (1,97 g, 20.9 mmol) in N.N-dimethylformamide (100 mL) was added sodium hydride (1,00 g, 20.9 mmol) at 0°C, 0, which was stirred for 5 minutes at 0°C, 2,6-Dibromopyridine (4,50 g, 18.0 mmol) was then added to this reaction solution at 0°C, and stirred for 40 minutes at room temperature. The reaction solution was then stirred for further 3 hours at 120°C. After allowing to room temperature, the reaction solution was partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chhoride, chied over anhydrous magnesium suitate and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl acetate = 8: 1) to obtain the title compound (3,85 g, 81 %).

¹H-NMR Spectrum (DMSO- d_0) δ (ppm): 7.02 (1H, dd, J = 0.55, 8.8 Hz), 7.11-7.14 (2H, m), 7.19-7.23 (1H, m), 7.38-7.43 (2H, m), 8.04 (1 H, dd, J = 2.6, 8.8 Hz), 8.25 (1 H, dd, J = 0.55, 2.6 Hz).

[Manufacturing Example 40-1-2] 6-Phenoxy-pyridine-3-carbaldehyde

05731

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[0574] To a solution of 5-bromo-2-phenoxy-pyrktine (3.85 g, 15.4 mmol) described in Manufacturing Example 40-1-1 in letralydrofuran (60 ml) was added n-buyl filhium (10.8 ml, 1.60 M hexane solution, 16.9 mmol) under nitrogen atmosphere at -78°C, Nichi was strifted for 56 minutes at -78°C. Nichi was strifted for 56 minutes at -78°C. Nichi was strifted for further 10 minutes at room temperature. After allowing to room temperature, the reaction solution at -78°C, which was stirred for further 10 minutes at room temperature. After allowing to room temperature and the student of the separated, washed with saturated aqueous softium choride, dried over anhydrous magnesium suitate and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane : ethly acateta et 5.11) to obtain the title compound (1.12 g, 37%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 7.04 (1 H, d, J = 8.6 Hz), 7.17 (2H, d, J = 7.5 Hz), 7.26-7.31 (1 H, m), 7.44-7.48 (2H, m), 8.19 (1 H, dd, J = 2.2, 8.6 Hz), 8.63 (1 H, d, J = 2.2 Hz), 9.99 (1 H, s).

[Manufacturing Example 40-1-3] 5-(2-Nitro-ethyl)-2-phenoxy-pyridine

[0575]

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J.Q.O

[0576] To a solution of 5-phenory-pyridine-3-carbaidehyde [1,12 g, 5.82 mmol) described in Manufacturing Example 40-1-2 in acetic acid (10 mt.) were added nitromethane (1,52 mt., 28.1 mmol) and ammonium acetate (666 mg. 1,1.2 mmol) under nitrogen atmosphere, which was stirred for 3 hours at 10°C. After being cooled to room temperature, the reaction solution was partitioned into water and eithyl acetate. The organic layer was separated, washed with saturated acueous sodium chloride, died over anhydrous magnesium suffale and filtered. The filter was concentrated under a reduced pressure. The resulting residue was dissolved in dimethyl sulfoxide (17 mt.) and acetic acid (3 mt.). Sodium borohydride (336 mg. 8.43 mmol) was added to this solution at room temperature white cooling appropriately, and stirred for 30 minutes at room temperature. The reaction solution was partitioned by addition of sodium hydrogencarbonate, water and eithyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, died over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane : ethyl acetate = 3 : 1) to obtain the tite compound (755 mc. 55%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.28 (2H, t, J = 7.1 Hz), 4.60 (2H, t, J = 7.1 Hz), 6.88 (1 H, d, J = 8.8 Hz), 7.11-7.14 (2H, m), 7.20-7.24 (1 H, m), 7.39-7.43 (2H, m), 7.55 (1 H, ddd, J = 0.37, 2.6, 8.4 Hz), 8.07 (1 H, d, J = 2.4 Hz).

[Manufacturing Example 40-1-4] (2-Phenoxy-pyridin-5-yl)-acetohydroximoyl chloride

[0577]

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[0578] To a solution of 5-(2-nitro-ethyl)-2-phenoxy-pyridine (753 mg, 3.08 mmol) described in Manufacturing Example 40-1-31 methanol (10 mL) was added lithium methoxide (234 mg, 6.16 mmol), which was stirred for 90 minutes at room temperature. The reaction solution was concentrated under a reduced pressure. The restating residue was suspended in a mixture solution of tetrahydrofuran (10 mL) and methylene chloride (10 mL). Titanium (IV) chloride (745 µL, 8.37 mmol) was added to the suspension under nitrogen atmosphere at -78°C, and stirred for 140 minutes at 0°C. The reaction solution was partitioned into water and ethyl acetate at 0°C. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (258 mg, 97%) as a crude product.

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.81 (2H, s), 6.99 (1H, dd, J = 0.73, 8.4 Hz), 7.09-7.12 (2H, m), 7.17-7.21 (1H, m), 7.38-7.42 (2H, m), 7.72 (1 H, dd, J = 2.6, 8.4 Hz), 8.03 (1 H, dd, J = 0.55, 2.6 Hz), 11.8 (1 H, s).

[Example 41] 3-(3-(4-(5-Fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0579]

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[0580] Tetrahydrofuran (10 mL) and 5 N aqueous sodium hydroxide solution (448 µL, 224 mmol) were acided to 4/5(2-amino-pyridin-3-yh)-isoxazoi-3-ylmethyh)-phenol (600 mg, 2.44 mmol) described in Manufacturing Exemple 5-1-1, which was irradiated by ultrasonic wave for 1 minute. The reaction solution was then concentrated under a reduced pressure to obtain a white solid 2-Choromethyl-5-fluoro-pyridine (259 mg, 2.46 mol) described in Manufacturing Example 41-2 and NN-dimethylformamide (10 mL) were added to the resulting white solid and stirred for 1 frour at 50°C. After being cooled to room temperature, the reaction solution was partitioned into water and ethyl acetate. The organic layer was separated and concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatorarphy (hebatan e: ethyl acetate 1: 11) to obtain the title compound (650 mg, 77%).

14-NMR Spectrum (DMSO-d₂) δ (ppm): 398 (2H, s), 5.15 (2H, s), 6.25 (2H, brs), 6.89 (1 H, dd, J = 4.8, 8.0 Hz), 6.79 (1 H, s), 6.99 (2H, dd, J = 4.8, 8.14), 7.79 (1 H, dd, J = 4.8, 8.14), 7.78 (1 H, dd, J = 2.8, 8.8 Hz), 7.89 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1 H, dd, J = 2.0, 7.8 Hz), 8.00 (1

[Manufacturing Example 41-1-1] (5-Fluoro-pyridin-2-yl)-methanol

[0581]

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[0582] To a solution of 2-brono-5-fluonopyridine (8.67 g, 20.8 mmnl) in bluene (100 mL) was added dropwise n-burly inhum (15.6 mL, 10.4 mkane solution, 25.0 mmol) under nitrogen atmosphere at 78°C, which was stirred for 30 minutes. N.N-Dinethylromamide (8.05 mL, 10.4 mmol) was added dropwise to this solution at -78°C, and stirred for 20 minutes at 0°C. This reaction solution was vigorously stirred after addition of water and tetrahydrofuran. The organic layer was separated, washed with water and saturated aqueous softium chloride, dried over anthydrous magnesium suffate and filtered. Sodium borohydride (1.58 g, 41.8 mmol) was added to the filtrate at 0°C, and stirred for 1 hours from temperature. This reaction solution was partitioned yet addition of water and tetrahydrofuran. The organic lost was separated, washed with saturated aqueous soldium bloride, dried over anthydrous angressium suffate and filtered. The filtrate was concentrated under a reduced pressure. The resulting residue was purified by NH side gel column chromatography (hazare : citalty teters = 1.2 to doubt in the tills commount (94.5 m. 3.8%L).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 4.75 (2H, s), 7.29 (1 H, dd, J = 4.4, 8.8 Hz), 7.43 (1 H, ddd, J = 2.8, 8.4, 8.4 Hz), 8.42 (1H, d, J = 2.8 Hz).

[Manufacturing Example 41-1-2] 2-Chloromethyl-5-fluoro-pyridine

[0583]

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[0584] To a solution of (5-fluoro-pyridin-2yl)-methanol (945 mg, 7.43 mnol) described in Manufacturing Example 41-1-1 in methylene chloride (70 mL) was added dropwise thionyl chloride (813 µL, 11.1 mmol) at room temperature, which was stirred for 30 minutes. This reaction solution was partitioned by addition of water, sodium hydrogencarbonate and methylene chloride. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium suifare and filtered. The fittlate was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (hexane: diethyl ether = 1:1) to obtain the title compound (761.1 mg, 2000).

¹H-NMR Spectrum (CDCl₆) δ (ppm): 4.67 (2H, s), 7.26-7.51 (2H, m), 8.43 (1 H, d, J = 2.8 Hz).

[Example 42] 3-(3-(4-(5-Methyl-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0585]

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10 [0866] 4-(5-(2-Amino-pyridin-3-y)lisoxazo-l-3-ylmethyl)-phenol (50 mg, 0.19 mmo) described in Manufacturing Example 5-1-1 and the 2-chloromethyl-5-methyl-pyridine (32 mg, 0.23 mmo)) described in Manufacturing Example 42:1-2 were used to obtain the title compound (23 mg, 33%) according to the methods similar to those of Example 10. 14-NMR Spectrum (DMSO-d₂) δ (ppm): 2.29 (8H, s), 3.95 (2H, s), 5.11 (2H, s), 6.25 (2H, brs), 6.80 (1 H, dd, J=4.8, 8.0+12), 6.79 (1 H, s), 6.97 (2H, d, J=8.4+12), 7.24 (2H, d, J=8.4+12), 7.38 (1 H, d, J=6.0+2), 7.62 (1 H, d, J=6.0+12), 7.86 (1 H, dd, J=1.6, 8.0+12), 8.40 (1 H, d

[0587] The starting material, 2-chloromethyl-5-methyl-pyridine was synthesized as follows.

[Manufacturing Example 42-1-1] (5-Methyl-pyridin-2-yl)-methanol

20 [0588]

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[0589] The title compound (1.1 g) was obtained according to the method described in Manufacturing Example 11-1-1 through Manufacturing Example 11-1-3.

39 1H-NMR Spectrum (DMSO-d₆) 8 (ppm): 2.27 (3H, s), 4.45 (2H, d, J=5.6Hz), 5.31 (1 H, t, J=5.6Hz), 7.34 (1 H, d, J=8.0Hz), 7.59 (1 H, dd, J=1.6, 8.0Hz), 8.31 (1 H, d, J=1.6Hz).

[Manufacturing Example 42-1-2] 2-Chloromethyl-5-methyl-pyridine

35 [0590]

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[0591] A mixed solution of (6-methyl-pyridine-2-yl)-methanol (500 mg, 4.1 mmol) described in Manufacturing Example 1-1-1, thiony bloride (0.56 mL, 8.1 mmol) and methylene chloride (10 mL) was stirred for 5 minutes under reflux. The reaction solution was cooled to room temperature and concentrated under a reduced pressure. The resulting residue was partitioned into dietrly either and saturated sodium blosmonates solution. The organic layer was separated and passed through a glass filter lined with silica gel (eluted with ethyl acctate). The ebute was concentrated to obtain the title compound (440 mg, 76%) as a crude product. The resulting compound was used in the following reaction without further purifications.

[Example 43] 3-(3-(4-(4-Methyl-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0592]

[0583] To a tetrahydrofuran (7.00 mL) solution of (4-4c-methy-pyrdin-2-yloxymethyl) phemyl)-acetorydroximoyl chioride (270 mg, 0.930 mmol) described in Manufacturing Example 43-15 and 3-ethynyl-pyrdin 2-ylarnine (40.0 mg, 0.330 mmol) described in Manufacturing Example 1-2-2 was added triethylarnine (189 µL, 1.36 mmol) at room temperature, which was stirred at room temperature for 4 hours. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over arrhydrous magnesium sulfate, and filtered. The filtrate was evaporated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:3 -> 1:2) to obtain the title compound (28.9 m. 2.0.8%).

'H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.26 (3H, s), 4.03 (2H, s), 5.30 (2H, s), 6.25 (2H, brs), 6.88-6.70 (2H, m), 6.80 (1 H, s), 6.81-6.82 (1 H, m), 7.32 (2H, d, J=8.0Hz), 7.39 (2H, d, J=8.0Hz), 7.86-7.86 (1 H, m), 8.00-8.02 (1 H, m), 8.00-8.03 (1 H, m), 8.00-8.02 (1 H, m), 8.00-8.03 (

[0594] The starting material, (4-(4-methyl-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

25 [Manufacturing Example 43-1-1] 2-(4-Bromo-benzyloxy)-4-methyl-pyridine

[0595]

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[0596] To a mixture of 4-bromobenzyl alcohol (4.54 g, 24.3 mmol) and N,N-dimethylfornamide (50.0 mL) were added sodium hydride (1.00 g, 25.0 mmol, 60% in oil) was added at 0°C under intrope atmosphere, which was stirred for 50 minutes at room temperature. 2-Fluoro-4-methylypylide (1.80 g, 16.2 mmol) was then added thereto at 0°C, and stirred for 2 hours and 30 minutes at room temperature. Water was added to the reaction solution at room temperature, which was then extracted with eithy actacle. The organic layer was separated, washed with saturated aqueous sodium-choride, and filtered. The filtrate was evaporated under a reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetale: heptane = 1: 15) to obtain the title compound (£6 g, 58.8%).

11-NMR Spectrum (DCDL) § (ppm): 22 (814), 8, 36.04 (31 (14), 8, 10.60 (31 (14), 11, 11, 11, 11).

[Manufacturing Example 43-1-2] 4-(4-Methyl-pyridin-2-yloxymethyl)-benzaldehyde

m), 7.46-7.48 (2H, m), 8.00-8.01 (1 H, m).

[0597]

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[0598] To a tetrahydrofuran (160 mL) solution of 2/46-bronc-benzy/kory)-4-methylpyridine (5.70 g, 20.5 mmol) described in Manufacturing Example 43-11 was added dropwise n-butyl lithium (2.67 M n-hexane solution, 9.21 mL, 24.6 mmol) on a dry ice-ethanol bath (78°C) under introgen atmosphere, which was stirred for 20 minutes at -78°C. N.Ndimethylformamide (3.16 mL, 41.0 mmol) was then added dropwise thereto and stirred for 10 minutes at -78°C. N.Nreaction solution was allowed to room temperature, waster was added, and the solution was extracted with effy acetate. The organic layer was separated and washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: heptane = 1; 31 to obtain the title compound (2.68 g, 56.54%).

¹H-NMR Spectrum (CDCl₃) δ (ppm); 2.31 (3H, s), 5.45 (2H, s), 6.66-6.67 (1 H, m), 6.72-6.74 (1 H, m), 7.58-7.60 (2H, m), 7.65-7.88 (2H, m), 8.00-8.01 (1 H, m), 10.0 (1 H, s).

[Manufacturing Example 43-1-3] 4-Methyl-2-(4-((E)-2-nitro-vinyl)-benzyloxyl-pyridine

[05991

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[0800]. To an acetic acid (20.0 m.l.) solution of 4-(4-methyl-pyridin-2-yloxymethyl-benzaldehyled (2.60 g. 11.5 mmol) described in Manufacturing Example 43-1-2 were added nitromethane (3.50 g. 57.3 mmol) and ammonium acetate (1.75 g. 22.9 mmol) at room temperature under nitrogen atmosphere, which was stirred for 4 hours at 100°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was separated, washed with vater and saturated aqueous sodium chloride, died over enhydrous magnacium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.40 g) as a crude implicit.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.28 (3H, s), 5.39 (2H, s), 6.75 (1 H, m), 6.84-6.85 (1 H, m), 7.50-7.53 (2H, m), 7.85-7.87 (2H, m), 8.00-8.02 (1H, m), 8.13 (1 H, d, J=13.6Hz), 8.23 (1 H, d, J=13.6Hz).

[Manufacturing Example 43-1-4] 4-Methyl-2-(4-(2-nitro-ethyl)-benzyloxy) pyridine

[0601]

[0602] To a dimethyl sulfoxide (50 mL) solution of 4-methyl-2-(4-(E)-2-mitto-vinyl)-benzyloxyl-pyridine (3.10 g. 11.5 mmol) described in Manufacturing Example 49-1-3 and acetic acid (3.10 mL) was added sodium borohydride (733 mg. 18.4 mmol) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 10 minutes. Water was then added dropwise into the reaction solution at room temperature while cooling appropriately, and the reaction mixture was extracted with eithyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1: 5 → 1: 2) to obtain the title compound (1.10 g. 35.1 %).

1H-NMR Spectrum (DMSO-d_e) δ (ppm): 2.27 (3H, s), 3.22 (2H, t, J=6.8Hz), 4.84 (2H, t, J=6.8Hz), 5.29 (2H, s), 6.69 (1

H, s), 6.82 (1 H, d, J=5.2Hz), 7.27 (2H, d, J=8.0Hz), 7.37 (2H, d, J=8.0Hz), 8.02 (1 H, d, J=5.2Hz).

[Manufacturing Example 43-1-5] (4-(4-Methyl-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride

5 [0603]

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15 [0604] To a methanol (10.0 mL) solution of 4-methyl-2-(4-(2-nitro-ethyl-)-benzyloxy)pyridine (500 mg. 1.84 mmol) described in Manufacturing Example 43-14 was added lithium methoxide (140 mg. 3.88 mmol) under nitrogen atmosphere at room temperature, which was stirred for 30 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure, and anhydrous dichloromethane (10.0 mL) and anhydrous tetrahyrdruran (5.00 mL) were added to the residue. Titinatine (fl.) which was added dropwise into the reaction mixture on a dry ice-ethanol bath (78°C), and stirred for 45 minutes at 0°C and then for 60 minutes at comit emperature. Water, ethyl acetate and tetrahydrotran were added to the reaction mixture on an ice bath (0°C), and the organic layer was separated. The organic layer was washed with water and saturated aquieous sodium chioride, direid over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (490 mg. 75.5%) as a crude product.

1H-NMR Spectrum (DMSO-d_θ) δ (ppm): 2.27 (3H, s), 3.82 (2H, s), 5.31 (2H, s), 6.70 (1 H, s), 6.82-6.84 (1 H, m), 7.24-7.28 (2H, m), 7.39-7.41 (2H, m), 8.01-8.03 (1 H, m), 11.73 (1 H, s).

[Example 44] 3-(3-(4-(5-Methyl-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

30 [0605]

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[0606] To a tetrahydrofuran (7.00 mL) solution of (4-(5-methyl-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride (248 mg, 0.846 mmo)) described in Manufacturing Example 44-1-5 and 3-ethynyl-pyridin-2-ylamine (40.0 mg, 0.339 mmo)) described in Manufacturing Example 1-2-2 was added thethyralmine (189 ML, 1.36 mmo) at room temperature, which was stirred for 4 hours at room temperature. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous socium chloride, dried over anhydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:3-+1:2) to obtain the title compound (2.1 mg, 1.6 3%).

¹H-NMR Spectrum (DMSO-d_b) 8 (ppm): 2.20 (3H, s), 4.03 (2H, s), 5.28 (2H, s), 6.25 (2H, brs), 6.68-6.71 (1 H, m), 6.75-6.77 (1 H, m), 8.81 (1 H, s), 7.32 (2H, d, J=8.0Hz), 7.39 (2H, d, J=8.0Hz), 7.52-7.55 (1H, m), 7.85-7.88 (1 H, m), 7.96-7.97 (1 H, m), 8.08-8.09 (1H, m).

[0607] The starting material, (4-(5-methyl-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

55 [Manufacturing Example 44-1-1] 2-(4-Bromo-benzyloxy)-5-methyl-pyridine

[0608]

[869] To an NN-dimetrylformamide (80.0 mL) solution of 4-bromobenzyl alcohol (4.54 g, 2.4.3 mmol) was added sodium hydride (1.00 g, 25.0 mmol). 60% in bill under nitrogen atmosphere at 0°C, which was altred for 50 minutes at room temperature. 2-Fluoro-5-methylpyridine (1.80 g, 16.2 mmol) was then added at 0°C, and stirred for 5 hours at room temperature. Water was added to the reaction solution at room temperature, which was then extracted with ethyl accetate. The organic layer was separated and washed with suttrated aqueous sodium chloride, and the solvent was exporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl accetate: heptane = 1: 15) to obtain the title compound (26.7 g, 58.3%).

1H-NMR Spectrum (CDCl₃) 8 (ppm): 2.24 (3H, s), 5.30 (2H, s), 6.70-6.72 (1 H, m), 7.31 -7.33(2H, m), 7.38-7.41 (1 H, m), 7.46-7.49 (2H, m), 7.95-7.96 (1 H, m).

[Manufacturing Example 44-1-2] 4-(5-Methyl-pyridin-2-yloxymethyl)-benzaldehyde

20 [0610]

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[0611] To a tertahydrofuran (150 ml.) solution of 2-(4-brome-benzyloxy)-5-mathylpyridine (5.40 g., 19.4 mmol) described in Manufacturing Example 44-1-1 was added dropwise n-butyl lithium (2.67 Mn -hexane solution, 8.73 ml., 23.3 mmol) on a dry lice-ethanol bath (-78°C) under nitrogen atmosphere, which was stirred for 30 minutes at -78°C. N/N-dimethylformamide (2.99 ml., 38.8 mmol) was then added dropwise thereto, which was stirred for 10 minutes at -78°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acteta. The organic layer was separated and washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: heptane = 1 : 6-1 : 4) to obtain the title compound (2.93 g. 66.5%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.21 (3H, s),5.41 (2H, s), 6.72-6.74 (1H, m), 7.38-7.41 (1H, m), 7.56-7.58 (2H, m), 7.83-7.85 (2H, m), 7.92-7.93 (1 H, m), 9.97 (1 H, s).

[Manufacturing Example 44-1-3] 5-Methyl-2-(4-((E)-2-nitro-vinyl)-benzyloxy)-pyridine

[0612]

[0613] To an acetic acid (20.0 m.l.) solution of 4-(5-methyl-ypirdin-2-yloxymethyl)-benzaldehyle (2.35 g, 12.9 mmol) described in Manufacturing Example 44-1-2 were added nitromethane (3.94 g, 6.45 mmol) and ammonium acetate (1.99 g, 28.8 mmo) under nitrogen atmosphere at room temperature, which was stirred for 2.5 hours at 100°C. Water and ethy acetate were added to the reaction mixture, and the organic layer was varietated with eithyl acetate. This organic layer was variety with water and saturated adventous sodium chloride, dried over an arwindrous manufacture. Buttlets, and

filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.50 g) as a crude product.
'H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.21 (3H, s), 5.38 (2H, s), 6.82-6.84 (1 H, m), 7.52 (2H, d, J-8.447), 7.55-7.58 (1 H, m), 7.52 (2H, d, J-8.447), 7.55-7.58 (1 H, m), 7.87 (2 H, d, J-8.447), 7.85-7.59 (1 H, m), 7.87 (2 H, d, J-8.447), 7.85-7.87 (1 H, m), 7.87 (2 H, d, J-8.447), 7.85-7.87 (1 H, m), 7.87 (2 H, d, J-8.447), 7.85-7.87 (1 H, m), 7.87 (2 H, d, J-8.447), 7.85-7.87 (1 H, m), 7.87 (2 H, d, J-8.447), 7.85-7.87 (1 H, m), 7.87 (1 H, d, J-8.447), 7.85-7.87 (1 H, m), 7.87 (1 H, d, J-8.447), 7.85-7.87 (1 H, m), 7.87 (1 H, d, J-8.447), 7.85-7.87 (1 H, J-8.447), 7.85-7.87 (1 H,

5 [Manufacturing Example 44-1-4] 5-Methyl-2-(4-(2-nitro-ethyl)-benzyloxy)pyridine

[0614]

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[0615] To a dimetrity surfoxide (40 0 mL) solution of 5-metrity-2-(4-((E)-2-nitro-winyl)-benzyloxy)-pyridine (3.50 g. 12.8 mmo)) described in Manufacturing Exemple 44-1-3 and acetic acid (3.50 mL) was added sodium borohydride (92.2 mg. 20.6 mmo)) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 10 minutes. Water was then added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 1.4) to obtain the title compound (1.91 o. 5.4.3%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.20 (3H, s), 3.22 (2H, t, J=6.8Hz), 4.84 (2H, t, J=6.8Hz), 5.27 (2H, s), 6.76-6.78 (1 H, m), 7.27 (2H, d, J=8.0Hz), 7.36 (2H, d, J=8.0Hz), 7.52-7.55 (1 H, m), 7.97-7.98 (1 H, m).

[Manufacturing Example 44-1-5] (4-(5-Methyl-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride

[0616]

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[0617] To a methanol (30 mL) solution of 5-methyl-2-(4-(2-hitro-ethyl)-benzyloxy)pyridine (700 mg, 2.57 mmol) described in Manufacturing Example 441-4 was added tilhum methodid (195 mg, 5.14 mmol) under introgen atmosphera at room temperature, which was atfirmed for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure, and entrydrous dichioromethane (15.0 mL) and entrydrous tetrahydrofuran (10.0 mL) were added to the residue. Titanium (IV) chloride (804 µL, 8.22 mmol) was added dropvise into the reaction mixture on a try les-ethanol bath (78°C), and then sizred for 45 minutes at room temperature. Water, ethyl acetate. This organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous megnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the tile compound (560 mg, 76.1 %) as a rew product. 11-H-NIMR Spectrum (DMSO-04) 8 (ppm): 202 (341, 8), 3.81 (2H, 8), 5.29 (2H, 8), 6.77-6.79 (1 H, m), 7.25 (2H, d, J=8.0Hz), 7.40 (2H, d. 3.6.0Hz), 7.57-95 (1 H, m), 7.7-25 (1

[Example 45] 3-(3-(4-(6-Fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0618]

10 [0619] Tetrahydrofuran (3 mL) and a 5 N aqueous sodium hydroxide solution (36.0 μ,L.). 18 mme) were acided to 4-(5-(2-amino pydinG-4y)-bacoayacia 9-yimehyly-pheno (48.2 mg.). 6.18 mme) described in Manufacturing Example 5-11, which was dissolved by irradating ultrasonic wave to 1 minute. The reaction mixture was then concentrated under a reduced pressure to obtain a white solid. This solid and 2-chloromethyl-6-fluoro-pyridine (63.2 mg., 0.49 mmo) described in Manufacturing Example 45-11 were added to NN-dimethylformamide (3 mL), which was stirred for 3 hours at room 15 temperature. This mixture was partitioned into water and ethyl acetate. This organic layer was separated, washed with water and saturated aqueous sodium chloride, dired over anhylcrous magnessum suitale, and filtera. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane : ethyl acetate = 1:1) to obtain the tible commound (47.9 mg., 89%).

1H-NMR Spectrum (CDCl₃) 8 (ppm): 4.00(2H, s), 5.12(2H, s), 5.40(2H, br s), 6.24(1 H, s), 6.71 (1 H, dd, J=4.8, 7.6Hz), 6.87(1 H, dd, J=2.8, 8.4Hz), 5.94(2H, d, J=8.8Hz), 7.40-7.42(1H, m), 7.70(1H, dd, J=1.6, 7.6Hz), 7.81 (1H, a, J=8.0Hz), 8.13(1H, dd, J=1.6, 8.8Hz)

[0620] The starting material, 2-chloromethyl-6-fluoro-pyridine, was synthesized as follows.

[Manufacturing Example 45-1-1] 2-Chloromethyl-6-fluoro-pyridine

[0621]

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[0822] A mixture of 2-fluore-6-methyleyridine (420 mg, 3.78 mmol), N-bhionsuccimide (757 mg, 5.67 mmol), 75% bearzoy leprovide (24.4 mg, 0.08 mmol), acel sect socil (13 gL, 0.23 mmol) and eacelonitie (7 mL) was sirred for 3 hours and 30 minutes at 85°C. The reaction mixture was cooled, water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: vall yet) acetate = 1:1) to obtain the title compound (370.7 mg, 67%). H-NMR Spectrum (DMSO-0.4) 50 pmm): 4.75 (21 st, 9.1, 7.17-7.19 (1.4 m), 7.67-7.85 (14 m, m), 8.02-8.08 (14 m, m).

[Example 46] 3-(3-(4-(5-Methyl-furan-2-ylmethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0623]

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[0824] To a mixture of (4-(6-methyl-turan-2-ylmethyl-)-plenyl)-acetohydroximoyl othoride (11 mg, 0.043 mmo) described in Manufacturing Example 46-16 and tetrihydrotrian (1 ml.) were added 5-ethymyl-pydrind-2-ylamine (4.0 mg, 0.034 mmo)) described in Manufacturing Example 1:2-3 and triethylamine (9.4 µL, 0.088 mmol) at room temperature, within the was third of the 3 ml ad 5°C. The reaction mixture was cooled to room temperature, water was added at the

same temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatorraphy (ethyl acetate: heptane = 2: 31) to other in the title compound (5.1 m. 4.1 %).

¹H-NMR Spectrum (CDC₁₉) δ (ppm): 2.24 (3H, s), 3.90 (2H, s), 4.03 (2H, s), 5.53 (2H, br.s), 5.85 (1 H, d, J=2.9Hz), 5.87 (1 H, d, J=2.9Hz), 6.26 (1 H, s), 6.72 (1 H, dd, J=5.0, 7.6Hz), 7.21 (4H, s), 7.72 (1 H, d, J=7.7Hz), 8.12 (1 H, dd, J=1.8, 4 Hz)

[0625] The starting material, (4-(5-methyl-furan-2-ylmethyl)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

10 [Manufacturing Example 46-1-1] 4-(Hydroxy-(5-methyl-furan-2-yl)-methyl)-benzaldehyde

[0626]

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[0627] To a mixture of 4-bromobenzaldehyde dimethyl excell [2.0 mL, 1.2 mmol) and diethyl ether (3.0 mL), was added dropwise r-butyl filtim (1.6 th. hexane solution, 9.0 mL, 1.4 mmol) at 72°C, which was stirred for 20 minutes at the same temperature. 5-Methylfurfural (1.3 mL, 13 mmol) was added dropwise into the reaction mixture at that temperature, and stirred for 50 minutes at 0°C. Water and ethyl accetate were added to extract the reaction mixture regarding and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: heptane = 1:2) to obtain the title compound (320m. 12%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.28 (3H, s), 5.86 (1 H, s), 5.90-5.91 (1 H, m), 5.98 (1H, d, J=3.1 Hz), 7.63 (2H, d, J=8.4Hz), 7.89 (2H, d, J=7.9Hz), 10.03 (1 H, s).

[Manufacturing Example 46-1-2] (4-(5-Methyl-furan-2-ylmethyl)-phenyl)-methanol

[0628]

[0629] To a mixture of lithium aluminumhydride (230 mg, 4.9 mmol) and tetrahydrofuran (15 mL) was added aluminum chloride (380 mg, 6.2 mmol) at 0°C, which was stirred for 30 minutes at room temperature. A humber of 4-(hydrosy-6-methyl-branz-gl-h)methyl-branzladehyde (320 mg, 1.5 mmol) described in Manufacturing Example 46-1-1 and tetrahydrofuran (5 mL) was added dropwise into the reaction mixture at 0°C, and stirred for 2 hours at that temperature. A 28% aqueous ammonia acultion was added dropwise into the reaction mixture at the same temperature to quench the excess reagent. The reaction mixture was cooled to room temperature, and filtered by being bassed through a Cellet bed. The filtrate was concentrated under a reduced pressure to obtain the title compound (330 mg) as a crude product. This compound was used in the following reaction without tuther purification.

[Manufacturing Example 46-1-3] 4-(5-Methyl-furan-2-ylmethyl)-benzaldehyde

[0630]

[0631] To a mixture of (4-(5-methyl-furan-2-ylmethyl)-phenyl)-methanol (350 mg, 1.7 mmol) obtained in Manufecturing Example 46-1-2 and dichloromethane (10 mL) was added manganese dioxide (3.5 g, 4.7 mmol) at room temperature. The reaction mixture was filtered through a Cellep aga, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: hebsten = 151 to obtain the rifte compound (100 mc, 29%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 2.25 (3H, s), 3.99 (2H, s), 5.876-5.883 (1 H, m), 5.92 (1 H, d, J=3.1 Hz), 7.39-7.41 (2H, m), 7.81-7.83 (2H, m), 9.99 (1 H, s).

[Manufacturing Example 46-1-4] 2-Methyl-5-(4-((E)-2-nitro-vinyl)-benzyl)-furan

[0632]

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[0633] To a mixture of 4-(6-methyl-furan-2-yimethyl-benzaldehyde (96 mg. 0.48 mmol) described in Manufacturing Example 48-13 and acetic acid (1 mt.) were added nitromethene (190 µL, 3.6 mmol) and ammonium acetate (110 mg. 1.4 mmol) at room temperature, which was stirred for 3 hours at 10°C. The reaction mixture was cooled to room temperature, and extracted by addition of water and ethyl acetate. The organic layer was washed with saturated aqueous acidum choirde and dried over magnesieum suitlare. The fiftrate was concentrated under a reduced pressure to obtain the title compound (120 mg) as a crude product. This compound was used in the following reaction without further ourification.

Manufacturing Example 46-1-5] 2-Methyl-5-(4-(2-nitro-ethyl)-benzyl)-furan

106341

[0635] To a mixture of 2-methyl-5-(4-((E)-2-nitro-vinyl)-benzyl)-furan (120 mg) described in Manufacturing Example 46-1-4, acetic acid (0.2 mL) and dimethyl sulfoxide (3.4 mL) was added sodium borrhydride (29 mg, 0.77 mmo) at room temperature with cooling appropriately, which was stringed for 2 minimizes at mon temperature. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by neutral silica gel column chromatography (ethyl sectate) retotate = 1: 510 obtain the title compound (90 mg. 77%).

 $^{1}\text{H-NMR Spectrum (CDCl}_{2}) \ \delta \ (\text{ppm}); 2.24 \ (3\text{H, s}), 3.30 \ (2\text{H, t, J}=7.4\text{Hz}), 3.89 \ (2\text{H, s}), 4.59 \ (2\text{H, t, J}=7.4\text{Hz}), 5.85 \cdot 5.87 \ (2\text{H, m}), 7.14 \ (2\text{H, d, J}=8.2\text{Hz}), 7.20 \ (2\text{H, d, J}=8.2\text{Hz}).$

55 [Manufacturing Example 46-1-6] (4-(5-Methyl-furan-2-ylmethyl)-phenyl)-acetohydroximoyl chloride

[0636]

[0637] To a mixture of 2-methyl-5-(4-[2-nitro-ethyl-benzyl)-furan (87 mg, 0.36 mmol) described in Manufacturing Example 48-1-5 and methanol (2 mL) was added lithium methoxide (27 mg, 0.71 mmol) at room temperature, which was stirred for 15 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure. Titanium (IV) chloride (86 µL, 0.78 mmol) was added at -78°C to a mixture of the resulting residue, methylene chloride (2 mL) and tehralyhorduran (1 mL), which was stirred for 1 hour at 0°C. The reaction mixture was cooled to -78°C, water (5 mL) was added, and the temperature was gradually raised to room temperature. The reaction mixture was about 5. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. Thereafor, the organic layer was filtered and the filtrate was concentrated under a reduced pressure to obtain the title compound (79 ms, 84%).

¹H-NMR Spectrum (CDCl_o) δ (ppm): 2.24 (3H, s), 3.78 (2H, s), 3.90 (2H, s), 5.85-5.87 (2H, m), 7.20 (4H, s).

[Example 47] 3-(3-(4-(2-Methyl-pyridin-4-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0638]

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[0639] (2-Methyl-pyridin-4-yl)-methanol (40 mg, 0.33 mmol) described in Manufacturing Example 47-1-1, thionyl chloridde (0.047 ml, 0.65 mmol) and methylene chloride (4.0 ml) were stirred for 5 minutes at 80°C. Sodium bloarbonate solution and ethyl acetate were added to separate the reaction solution, and the ethyl acetate layer was dried over sodium suifate. The solvent was evaporated under a reduced pressure to obtain 4-chloromethyl-2-methyl-pyridine as a crude product.

[0640] 2. N Sodium hydroxide (0.16 m.), 0.32 mmol) and methanol (1.0 ml) were added to dissolve 4.[5:[2-aminopyridin-3-y])iscoxazol-3-yimethyl)-phenol (87 mg, 0.33 mmol) described in Manufacturing Example 5-1-1, and methanol was avaporated under a reduced pressure. A solution of the aforementioned 4-chloromethyl-2-methyl-pyridin dessolved in dimethyl-0-manufact (1 ml) was added to the residue and stirred for 10 minutes at 60°C. Water and ethyl acettee were added to experted the reaction solution, the resulting thyll sectles yet was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 1: 3) to obtain the title compound (47 m.0.39%).

14-1MR Spectrum (DMSO-d₆) δ (pmp): 2.47 (3H, s), 3.96 (2H, s), 5.11 (2H, s), 6.26 (2H, brs), 6.68 (1 H, dd, J=4.8, 8.0Hz), 6.79 (1 H, s), 6.97 (2H, d, J=8.8Hz), 7.20 (1 H, d, J=5.2Hz), 7.25 (2H, d, J=8.8Hz), 7.29 (1 H, s), 7.86 (1 H, dd, J=2.0, 8.0Hz), 8.08 (1 H, dd, J=2.0, 4.8Hz), 8.42 (1 H, d, J=5.2Hz).

[0641] The starting material, (2-methyl-pyridin-4-yl)-methanol, was synthesized as follows.

[Manufacturing Example 47-1-1] (2-Methyl-pyridin-4-yl)-methanol

[0642]

[0643] The title compound (200 mg) was obtained according to the methods similar to those of Manufacturing Example 11-1-1 through Manufacturing Example 11-1-3,

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.45 (3H, s), 4.50 (2H, d, J=5.2 Hz), 5.37 (1 H, t, J=5.2 Hz), 7.11 (1 H, d, J=5.2 Hz), 7.18 (1 H, s), 8.36 (1 H, d, J=5.2 Hz).

[Example 48] 3-(3-(5-p-Tolyloxy-thiophen-2-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

5 [0644]

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[0645] To a tetrahydrofuran (7.00 mL) solution of (5-ptolyloxy-thiophen-2-yf)-acetohydroximoyl chloride (191 mg, 0.678 mmol) described in Manufacturing Example 46-1-5 and 3-ethynyl-pyridin-2-yfamine (40.0 mg, 0.339 mmol) socioed in Manufacturing Example 1-2-3 was added tetrihyalmine (189 mg, 1.188 mmol) a froom temperature, which was stirred for 4 hours at room temperature. Water was added to the reaction solution at room temperature, which was then extracted with entity acetale. The organic layer was weshed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica get column chromatography (ethyl scatate: heptame = 1:3) to obtain the titic compound (2.03 mg, 1.65%). "H-NMR Spectrum (DNSO-d₂) 6 ppm; 2.32 (9.14, s), 4.14 (214, s), 5.54 (214, ms), 6.34-6.36 (1 H, m), 6.40 (1 H, s), 6.82-6.83 (1 H, m), 6.73-6.77 (1 H, m), 6.90-7.00 (2H, m), 7.11-7.13 (2H, m), 7.76-7.76 (1 H, m), 8.14-8.15 (1 H, m), 6.90-6.01 (1 H,

[Manufacturing Example 48-1-1] 5-p-Tolyloxy-thiophene-2-carbonitrile

[0647]

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[0648] To a dimethyl sulfoxide (100 ml.) solution of 5-nitro-2-thiophenecarbonitrile (8.30 g. 40.9 mmol) were added p-cresol (8.85 g. 81.8 mmol) and potassium carbonate (11.3 g. 81.8 mmol) under nitrogen atmosphere, which was stirred for 5 hours at 80°C. The reaction solution was cooled to room temperature, and extracted with ethyl acetate after addition of water. The organic layer was washed with saturated aqueous sodium orbioride, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:3 --2:1) to totain the title compound (6 95 or 7.89 x 10.80 x 10.80

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.36 (3H, s), 6.38-6.39 (1 H, m), 7.03-7.05 (2H, m), 7.18-7.20(2H, m), 7.33-7.35 (1 H, m).

[Manufacturing Example 48-1-2] 5-p-Tolyloxy-thiophene-2-carbaldehyde

[0649]

[0650] To a tetrahydrofuran (7.0 mt) solution of 5-p tolyloxythiophene: 2 carbontrine (2.00 g, 9.28 mmo) described in Manufacturing Example 48-1-thes added dropwise dissolutyl aluminum hydride (0.97 Mr. hexane solution, 2.3 9 mL, 23.2 mmo) on a dry loe-ethanol bath (-78°C) under nitrogen atmosphere, which was stirred for 3 hours at room temperature. The reaction mixture was cooled to room temperature and extracted with ethyl acetate after addition of water. The organic layer was vashed with saturated aquoes sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : heptane = 1 : 5) to obtain the title compound (9.88 m., 4.72%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.36 (3H, s),6.47 (1 H, d, J=4.0Hz), 7.08 (2H, d, J=8.0Hz), 7.20 (2H, d, J=8.0Hz), 7.51 (1 H, d, J=4.0Hz), 9.69 (1 H, s).

[Manufacturing Example 48-1-3] 2-((E)-2-Nitro-vinvl)-5-p-tolyloxy-thiophene

[0651]

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[0852] To an acetic acid (20.0 ml.) solution of 5-p-tolyloxy-thiophene-2-carbaldehyde (2.30 g, 10.5 mmp) described in Manufacturing Example 48-1-2 were added nitromethane (3.20 g, 52.5 mmo) and ammonium acetate (1.62 g, 21.0 mmo) under nitrogen atmosphene at room temperature, which was stirred for 2.5 hours at 100°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with water and acturated aqueous sodium chloride, diried over annivorous magnesium sulfate, and filtered. The solvent was evaporated from the filtrate under a reduced pressure to obtain the title compound (2.50 g) as a crude product. 1H-NMR Spectrum (DMSO-dg) 6 (ppm): 232 (3H, s), 6.70 (1 H, d, J=4.0Hz), 7.18 (2H, d, J=8.0Hz), 7.28 (2H, d, J=12.8Hz).

[Manufacturing Example 48-1-4] 2-(2-Nitro-ethyl)-5-p-tolyloxy-thiophene

[0653]

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[0654] To a dimethyl sulfoxide (30.0 m.L) solution of 2-{(E)-2-nitro-vinyl)-5 p-tolyloxythiophene (2.50 g, 9.57 mmol) described in Manufacturing Example 48-1-3 and acotic acid (2.50 m.L) was added sodium borohydride (610 mg, 20.5 mmol) at room temperature while cooling appropriately under nitrogen almosphere, which was street of 50 minutes at room temperature. Water was then added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure and the residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 1 : 4) to obtain the title compound (1.20 a. 4.76%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.28 (3H, s), 3.33 (2H, t, J=6.4Hz), 4.81 (2H, t, J=6.4Hz), 6.45-6.46 (1 H, m), 6.67-6.69 (1 H, m), 6.98-7.00 (2H, m), 7.17-7.20 (2H, m).

[Manufacturing Example 48-1-5] (5-p-Tolyloxy-thiophen-2-yl)-acetohydroximoyl chloride

[0655]

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CLYS O

[0656] To a methanol (10.0 mL) solution of 2-(2-nitro ethyl)-5 p-tolytoxy thiophene (500 mg, 1,90 mmol) described in Manufacturing Example 48-1-4 was added lithium methoxide (144 mg, 3,80 mmol) under nitrogen atmosphere at room temperature, which was stiered for 30 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure, and anhydrous dichloromethane (15.0 ml) and anhydrous trainly riorfuran (10.0 ml) were added to the reaction mixture on a dry ice-ethanol bath (78°C), which was stirred for 45 minutes at room temperature. Water, ethyl acetate and tetrahydrofuran were added to the reaction mixture on an ice bath (0°C), and the organic layer was exhancted with ethyl acetate. This organic layer was exhancted view to see that of the control of

¹H-NMR Spectrum (DMSO-d₀) δ (ppm): 2.28 (3H, s), 3.94 (2H, s), 6.48 (1 H, d, J=3.6Hz), 6.74 (1H, d, J=3.6Hz), 7.00-7.01 (2H, m), 7.18-7.20 (2H, m), 11.81 (1 H, s).

[Example 49] 3-(3-(4-(Pyridin-4-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

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W NH.

[0658] Tetrahydrofuran (3 mL) and a 5 N aqueous sodium hydroxide solution (224 µL, 0.11 mmol) were acided to 4-(5-(2-amino-pyridine-3-yh-soxazole-3-yhrethyl)-phenol (30 mg, 0.11 mmol) described in Manufacturing Example 5-1-1, which was dissolved by Irradiating ultrasonic wave for 1 minute. Next, the reaction solution was concentrated under a reduced pressure to obtain a white solid. The resulting solid was suspended in N, N-dimethylformamide (1 mL). Meanwhile, THF (369 µL, 0.31 mmol) were added to 4-(chloromethyl)-pyridine hydrochloride (50 mg, 0.39 mmol) and then the ogranic layer was separated to obtain a tetrahydrofuran solution of 4-(chloromethyl)-pyridine. A part of this tetrahydrofuran solution (224 µL) was added to the NN-dimethylformamide suspension prepared above, and stirred for 45 minutes at 60°C. This mixture was cooled to room temperature, and partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, died over anhydrouw magnesium sutlets, and filtered. The filtrate was concentrated under a reduced pressure and the residue was purified by NH silika gel column chromatography (ethyl scelate) to obtain the title compound (36 mg, 88%).

¹H-NMR Spectrum (DMSO-d_d) δ (ppm): 3.97 (2H, s), 5.17 (2H, s), 6.26 (2H, brs), 6.68-6.72 (1 H, m), 6.79 (1 H, s), 6.99 (2H, d, J=8.4Hz), 7.26 (2H, d, J=8.8Hz), 7.43 (2H, d, J=6.0Hz), 7.87 (1H, dd, J=2.0,7.6Hz), 8.09 (1 H, dd, J=1.6, 4.8Hz), 8.57 (2H, dd, J=1.6, 4.8Hz), 8.

[Example 50] 3-(3-(4-(Pyridin-3-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

5 [0659]

[0660] Tetrahydrofuran (3 mL) and a 5 N aqueous sodium hydroxide solution (22 4 μL, 0.11 mmol) were added to 4.(5 (2-amino pyridin-3 yl)-isoxazol-3 ylmethyl) phenol (30 mg, 0.11 mmol) described in Manufacturing Example 51-1, which was dissolved by irradialing ultrasonic wave for 1 minute. Next, the reaction solution was concentrated under a reduced pressure to obtain a white solid. This solid was suspended in N,N-dimethylformamide (1 mL). Meanwhile, THF (390 μL) and a 1 N aqueous social m hydroxide solution (390 μL, 0.93 mmol) were added to 3 -(choromethyl)pyrdine hydrochloride (50 mg, 0.39 mmol), and then the organic layer was separated to obtain a tetrahydrofuran solution of 3-(chloromethy)pyrdine. A part of this tetrahydrofuran solution (224 μL) was added to the N,N-dimethylformamide suspension prepared above, and stirred for 45 minutes at 60°C. This mixture was cooled to room temperature, and partitioned into water and ethyl sociatic. The organic layer was separated, washed with water and saturated aqueous solution room the solution of the solution

¹H-NMR Spectrum (DMSO-d₆) 8 (ppm): 3.97 (2H, s), 5.13 (2H, s), 6.25 (2H, brs), 6.67-6.74 (1 H, m), 6.78 (1 H, s), 7.00 (2H, d, J=8.0Hz), 7.26 (2H, d, J=7.6Hz), 7.40-7.46 (1 H, m), 7.85-7.89 (2H, m), 8.09 (1 H, d, J=4.8Hz), 8.54 (1 H, d, J=4.8Hz), 8.54 (1 H, d, J=4.8Hz), 8.54 (1 H, m), 7.85-7.89 (2H, m), 8.09 (1 H, d, J=4.8Hz), 8.54 (1 H, m), 7.85-7.89 (2H, m), 8.09 (1 H, d, J=4.8Hz), 8.54 (1 H, m), 7.85-7.89 (2H, m), 8.09 (2

[Example 51] 3-(3-(4-(4-Chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0661]

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NH. CI

[0862] Tetrahydrofuran (3 mL) and 5 N aqueous sodium hydroxide solution (22.4 µL, 0.11 mmol) were added to 4.6-(2-amino-pyridine-3-yl)-isoxazole-3-yimethyl)-phenol (30 mg, 0.11 mmol) described in Manufacturing Example 5-1-1, which was dissolved by irradiating ultrasenic wave for 1 minute. Next, the reaction solution was concentrated under a reduced pressure to obtain a white solid. An N.N-dimethyfformamide (1 mL) solution of 4-chiloro-2-chiloromethyl-pyridine (38.3 mg, 0.22 mmol) described in Manufacturing Example 5-11-2 was added to a suspension of this solid and N.N-dimethyfformamide (1 mL), which was stirred for 1 hour at 60°C. This mixture was cooled to room temperature, and a N.H-dimethyfformamide (1 mL), which was stirred for 1 hour at 60°C. This mixture was cooled to room temperature, and solution dinto water and ethyl acctate. The organio layer was separated, washed with water and saturated aqueous sodium chiloride, dried over arhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure and the residue was purified by NH sitica gel column chromatography (heptane: ethyl acctate = 1:1) to obtain the title compound (36.6 mg, 38%).

¹H-NMR Spectrum (DMSO-d₀) δ (ppm): 3.97 (2H, s), 5.17 (2H, s), 6.26 (2H, brs), 6.69 (1 H, dd, J=4.8, 8.0Hz), 6.79 (1 H, s), 7.01 (2H, d, J=8.4Hz), 7.26 (2H, d, J=8.4Hz), 7.51 (1 H, dd, J=2.0, 8.2Hz), 7.61 (1 H, d, J=2.0Hz), 7.87 (1 H, dd, J=2.0 Hz), 7.87 (1 H, dd, J=2.0 Hz), 8.08 (1 H, dd, J=2.0, 4.8Hz), 8.65 (1 H, d, J=2.2 Hz).

[0663] The starting material, 4-chloro-2-chloromethyl-pyridine, was synthesized as follows.

[Manufacturing Example 51-1-1] (4-Chloro-pyridin-2-yl)-methanol

[0664]

[0665] To a mixture of 4-chloro-2-picoline (1.0 g. 784 mmol) and dichloromethane (20 mL), was added m-chloroper-beracioe acid (3.5 g. 13.2 mmol) on an ice bath, which was stiffered for 1.5 hows at room temperature. Water and sodium hydrogencarbonate were added to the reaction, followed by extraction with dichloromethane. The organic layer was separated, washed with water and seturated acquouse sodium chloride, dried over analyticus magnesium suitate, and filtered. Acte (an hydride (20 mL) was added to the residue obtained by concentrating the filtrate under a reduced pressure, and this was stirred for 1 hourst 100°C. The reaction mixture was cooled to room temperature and concentrated under a reduced pressure. As N equicus sodium hydroxide solution (1.5 Tm. L. 78 rmmol) was added to a mixture of the resulting residue and methanol (20 mL) on an ice bath, which was stirred for 1.5 hours at room temperature. Water was added to the mixture, which was then extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueues sodium chloride, dired over analyticus magnesium suittle, and filtero. The filtrate was concentrated under a reduced pressure and the residue was purified by NH silica gel column chromatography (heptane : ethyl scettle s 6 : 11 to bothlat the this comound (200 m.n. 18%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 4.76(2H, s), 7.23-7.25(1H, m), 7.32-7.33(1H, m), 8.46(1 H, d, J=5.6Hz).

[Manufacturing Example 51-1-2] 4-Chloro-2-chloromethyl-pyridine

[0666]

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[0667] To a mixture of (4-chlorr-pyrdine-2y-)-methanol (146.8 mg, 1.0 mmol) described in Marufacturing Example 51-1-1 and toluene (3 mL) was added thonly Individe (112 µL, 15 mmol) on an ice bath, which was stirred for 1 hour 15 minutes at room temperature. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium suttee, and filtered. The fiftrate was concentrated under a reduced pressure and the residue was purified by NH silica gel column chromatography (heptane: ethyl scetate = 4: 1) to obtain the title compound (87 ms. 59%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 4.65(2H, s), 7.26-7.28(1 H, m), 7.52-7.53(1 H, m), 8.48(1H, d, J=5.6Hz).

[Example 52] 3-(3-(4-(6-Chloro-pyridin-2-vlmethoxy)-benzyl)-isoxazol-5-vl)-pyridin-2-vlamine

[0668]

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[0669] Tetrahydrofuran (3 mL) and a 5 N aqueous sodium hydroxide solution (22 4 µL, 0.11 mmol) were added to 4-(5-(2-amino-pyridin-3-y))isoxazol-3-ylmethyl): phenol (30 mg, 0.11 mmol) described in Manufacturing Example 5-1-1, which was dissolved by irradiating ultrasonic wave for 1 minute. The reaction solution was then concentrated under a reduced pressure to obtain a white solid. An NN-dimethylformamide (1 mL) solution of 2-chloro-6-chloromethyl-pyridime (88 3 mg, 0.22 mmol) described in Manufacturing Example 52-1-2 was added to a suspension of this solid and N,N-dimethylformamide (1 mL), which was stirred for 1 hour at 60°C. This mixture was cooled to room temperature and partitioned into water and ethyl acotate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dired over analyticous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 1:1) to obtain the title compound (38 5 ms, 98%).

1H-NMR Spectrum (DNSO-d_b) δ (ppm); 3.97(2H, s), 5.15(2H, s), 6.26(2H, brs), 6.69(1 H, dd, J=4.8, 8.0Hz), 6.79(1 H, s), 6.99(2H, d, J=8.4Hz), 7.26(2H, d), 7.46-7.52(2H, m), 7.85-7.92(2H, m), 8.08(1 H, dd, J=2.0, 4.8Hz), 0.06701 The starting material. 2-ohior-6-chloromethy-ordinal, was svirthestered as follows.

[Manufacturing Example 52-1-1] (6-Chloro-pyridin-2-yl)-methanol.

[0671]

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[6672] To a mixture of 2-chloro-E-methylpyrdine (1.0 g. 7.84 mmol) and dichioromethane (20 mL) was added m-chloroperbanzolc acid (3.5 g. 13.2 mmol) on an ice bath, which was stirred for 1.5 hours at 40°C. Water and sodium hydrogencarbonals were added to the reaction mixture, which was then extracted with dichioromethane. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dridd over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure. Acetic anhydride 20 mL) was added to the resulting residue and stirred for 1 hour at 100°C. The reaction mixture was cooled to room temperature and concentrated under a reduced pressure. A FN aqueous sodium hydroide southion (4m. 20.1 mmol) was added to a mixture of the resulting residue and methano (20 mL) on an ice bath, which was stirred for 30 minutes. Water was added to this mixture, which was then extracted with eithyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, died over anhydrous magnessum suifate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (neptane: ethyl acetate = 3 : 1) to obtain the title compound (200.0 mg. 18%).

¹H-NMR Spectrum (CDCl₃) ô (ppm): 3.08(1H, brs), 4.75(2H, d, J=5.2Hz), 7.23-7.27(2H, m), 7.64-7.69(1 H, m).

[Manufacturing Example 52-1-2] 2-Chloro-6-chloromethyl-pyridine

[0673]

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[0674] To a mixture of (6-chloro-pyridine-2-yl)-methanol (200 mg. 1.39 mmol) described in Manufacturing Example 52-11 and toluneo (3 mL) was added thionyl chloride (152 µL, 20 mmol) on an loe bath, which was attern for 2 hours at room temperature. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, which was then extracted with einlyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, died over analyticus magnesium suite, and filtere. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 4:1) to obtain the title compound (163.2 mg. 73%).

55 1H-NMR Spectrum (CDCl₃) δ (ppm): 4.64(2H, s), 7.29(1 H, d, J=8.0Hz), 7.44(1 H, d, J=7.6Hz), 7.70(1H, dd, J=7.6, 8.0Hz).

[Example 53]3-(3-(6-Phenoxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0675]

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N NH,

[0676] To a tetrahydrofuran (2 mL) solution of (2-phenoxy-pyridin-5-yf)-acetohydroximoyl chloride (100 mg, 0.381 mmol) described in Marufacturing Example 40-1-4 and 3-ethynyl-pyridin-2-ylamine (30 mg, 0.25 mmol) described in Marufacturing Example 1-2-9 was added trietylpamine (71 µL, 0.51 mmol) under introgen atmosphere, which was stried for 3 hours at 50°C. Water was added to the reaction moture at room temperature, which was then extracted with either adsurated apuecus sodium chloride, dried over annydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silicage dorumar choreadorpshy (ethyl acetate: methanol = 10 : 1) to obtain the title compound (27 mg, 31 %). H-NNR Spectrum (DMSO-4g.) 5 (ppm)-4.02(21, 1), 6.26(21, 1), 6.86(11, 1), d., 1-4.7, 712, 6.83(11, 1), s. 9.84(11, 1), 1-4.7, 1-7.7, 1-6.7, 1-7.7, 1-7.8, 1-7.7, 1-7.8, 1-7.7, 1-7.8, 1-7.7, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8, 1-7.8,

Example 541 3-(3-(6-Phenoxymethyl-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0677]

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[0678] To a tetrahydrofuran (3.00 mL) solution of (6-phenoxymethyl-pyridin-3-yl-) acetohydroximoyl chloride (9.00 mg, 0.289 mmol) described in Manufacturing Example 54-16 and 3-ethynyl-pyridin-2-ylamine (20.0 mg, 0.169 mmol) described in Manufacturing Example 12-3 was added to tethylamine (70.7 µL, 0.507 mmol) at room temperature, which was stirred for 4.5 hours at 60°C. Water was added to the reaction solution at room temperature, which was stirred for 4.5 hours at 60°C. Water was added to the reaction solution at room temperature, which was the stirred and secure solution and intelled very annydrous magnesium sulfate, and the solvent was evenorated under a reduced pressure. The residue was purified by NH silica gle column chromatography (ethyl acetate : heptane 2 : 1 → 3 : 1) to obtain the title compound (4.00 mg, 6.69%). 1H-NMR Spectrum (DNSO-4) 6 (ppm): 4.10 (2H, s), 5.15 (2H, s), 6.27 (2H, brs), 6.69-6.72 (1H, m), 8.87 (1H, s), 5.98-5.09 (1H, m), 7.78-7.79 (1H, m), 7.86-7.88 (1H, m), 8.98-8.10 (1H, m), 8.98-8.99 (1H, m), 7.87-7.99 (1H, m), 7.88-7.88 (1H, m), 8.98-8.10 (1H, m), 7.88-7.89 (1H, m), 7.88-7.89 (1H, m), 8.98-8.99 (1H, m), 7.88-7.89 (1H, m), 7.88-7.89 (1H, m), 7.88-7.89 (1H, m), 8.98-8.99 (1H, m), 7.88-7.89 (1H, m

[0679] The starting material, (6-phenoxymethyl-pyridin-3-yl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 54-1-1] (5-Bromo-pyridin-2-yl)-methanol

[0680]

[0881] To a toluene (300 mL) solution of 2,5-dibromopyridine (10.0 g, 42.2 mmol) was added dropwise n-buyli lithium (2.55 M n-hexane solution, 18.2 mL, 46.4 mmol) on a dy ice-ethanol bath (-78°C) under nitrogen atmosphere, which was stirred for 2 hours at -78°C. Soldum borohydride (3.20 g, 84.4 mmol) and methanol (20.0 mL) were then added and stirred for 10 minutes at -78°C. Soldum borohydride (3.20 g, 84.4 mmol) and methanol (20.0 mL) were then added and stirred for 30 minutes at crown temperature. Water was added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: heptane = 1:1 → 2:1) to obtain the title compound (4.70 g, 59.2%).

¹H-NMR Spectrum (DMSO-d_e) δ (ppm): 4.54 (2H, d, J=5.6Hz), 5.28 (1 H, t, J=5.6Hz), 7.44-7.47 (1 H, m), 8.03-8.05 (1 H, m), 8.59-8.60 (1 H, m).

[Manufacturing Example 54-1-2] 5-Bromo-2-chloromethyl-pyridine hydrochloride

[0682]

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[0683] To a tolusine (20.0 mL) solution of (5-bromo-pyridin-2-yl)-methanol (4.70), 25.0 mmol) described in Menufacuring Example 54-11 was added droppies binloying foldoride (3.65 mL, 5.01 mmol) on an io bath (0.70) under introgen atmosphere, which was stirred for 5 minutes at room temperature. The solvent was evaporated under a reduced pressure to obtain the till compound (4.2 of 8.02 %) as a hydrochloridia.

1H-NMR Spectrum (DMSO-dc) & (ppm): 4.78 (2H, s), 7.55-7.57 (1H, m), 8.11-8.14 (1H, m), 8.70-8.72 (1H, m),

[Manufacturing Example 54-1-3] 5-Bromo-2-phenoxymethyl-pyridine

[0684]

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2 [0885] To an N,N-dimethyfromaminide (40.0 mL) solution of phenol (1.92, 2.0.4 mmol) was added sodium hydride (815 m, 20.4 mmol, 60% in 0.1) on a los bath (0°C) under infregoe atmosphere, which was stirred for 20 minutes at room temperature. To the reaction solution was then added a mixture of 5-bromc-2-chloromethyf-pyridine hydrochioride (4.2 g, 20.4 mmol) described in Manufacturing Example 541-12 and trehtylamine (28.0 mL, 20.4 mmol), which was stirred first of 30 minutes at room temperature and then for 45 minutes at 70°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was extracted with ethyl acetate. This organic layer was washed with water and saturated aquecus sodium choldride, dired over anhydrous magnesium sutflax, and filtered. The solvent was exported from the filtrate under a reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate: hectare = 1: 10 to obtain the title compound (4.0 g, 81.7%).

¹H-NMR Spectrum (CDCl₃) & (ppm): 5.15 (2H, s), 6.95-6.99 (3H, m), 7.25-7.31 (2H, m), 7.42-7.45 (1 H, m), 7.81-7.83 (1 H, m), 8.64-8.65 (1 H, m).

[Manufacturing Example 54-1-4] 6-Phenoxymethyl-pyridin-3-carbaldehyde

[0686]

[0687] To a diethyl ether (250 m.l.) solution of 5-bronn-2-phenoxymethyl-pyridine (4.40 g, 1.6. mmol) described in Manufacturing Example 54-1-3 was added n-bulyl lithium (2.55 M n-bexane solution, 8.46 ml., 21.6 mmol) on a dry locethanol bath (78°C) under introgen atmosphere, which was stirred for 40 minutes at -78°C. The reaction solution was (1.93 ml., 25.0 mmol) was then added dropwise thereto and stirred for 20 minutes at -78°C. The reaction solution was allowed to room temperature, where was added, and the solution was extracted with expl acetate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : heptane = 1 : 3) to obtain the title compound (1.00 q. 28.3%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 5.29 (2H, s), 6.97-7.01 (3H, m), 7.29-7.33 (2H, m), 7.73-7.75 (1 H, m), 8.19-8.21 (1H, m), 9.05-9.06 (1H, m), 10.12 (1 H, s).

20 [Manufacturing Example 54-1-5] 5-(2-Nitro-ethyl)-2-phenoxymethyl-pyridine

[0688]

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[0689] To a methanol (2.00 mL) solution of 6-phenoxymethy-byrdines-3-carbadehyle (1.00 g. 4.86 mmol) described in Marufacturing Example 5.4-1-4 was added filthum methoxide (2.14 mg. 0.56 mmol) under hitrogen atmosphere at room temperature. This was cooled to 0°C, and nitromethane (372 mg, 6.10 mmol) and lithium methoxide (1.83 mg, 5.07 mmol) were added and stirred for 10 minutes at room temperature. The reaction solution was then concentrated under areduced pressure. Tetrahyrdortung (2.00 mL) was added to the residue, and then acetic anhyrdide (6.24 g. 81.1 mmol) and siterly/amine (1.42 mL, 10.2 mmol) were added and stirred for 1 hour at 7°°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was exhated with water and saturated aqueous solium chloride, dried over anhyrdorus magnesium sulfate; and filtered. The solvent was evaporated from the filtrate under a reduced pressure. Methanol (2.00 mL) was added to the residue, and sodium borohyrdide (283 mg, 6.96 mmol) was then added on an ice bath (0°C). Following 5 minutes of stirring at 0°C, water was added dropwise at 0°C. The reaction mixture was estracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated from the filtrate under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate; a petitione 2.1 %). Obtains the tile compound (17 mg, 14.2%).

1H-NMR Spectrum (DMSO-0_d) δ (ppm): 3.25 (2H, t, J=6.8Hz), 4.91 (2H, t, J=6.8Hz), 5.14 (2H, s), 6.93-6.97 (1 H, m), 7.00-7.02 (2H, m), 7.27-7.31 (2H, m), 7.46-7.48 (1 H, m), 7.75-7.78 (1 H, m), 8.49-8.50 (1 H, m).

[Manufacturing Example 54-1-6] (6-Phenoxymethyl-pyridin-3-yl)-acetohydroximoyl

[0690] chloride

[0691] To a methanol (7.00 mL) solution of 5-(2-nitro-ethyl)-2-phenoxymethyl-pyridine (170mg, 0.658 mmol) described in Manufacturing Example 54-1-5 was added lithium methoxide (5.0 mg, 1.32 mmol) under nitrogen atmosphere at room temperature, which was stirred for 50 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure, and anhydrous dichloromethane (10.0 ml) and anhydrous tetrahydrofuran (5.00 ml) were added to the residue. Titenium (fly cholinde (32 th µ.2.11 mmol) was added dropwise into the reaction mixture on a dry ica-ethanol bath (7.9°C), which was stirred for 50 minutes at room temperature. Water, ethyl acetate and tetrahydrufuran were added to the reaction mixture on an ice bath (0°C), and the organic layer was extracted with ethyl acetate. This organic layer was washed with water and saturated equeous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated from the filtrate under a reduced pressure to obtain the title compound (189 m. og 2.8%) as a crude produced.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.90 (2H, s), 5.17 (2H, s), 6.93-6.97 (1 H, m), 7.01-7.03 (2H, m), 7.27-7.30 (2H, m), 7.49-7.51 (1 H, m), 7.72-7.74 (1 H, m), 8.49-8.50 (1 H, m), 11.83 (1 H, s).

[Example 55] 3-(3-(4-(6-Fluoro-pyridin-2-vloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-vlamine

[0692]

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Is 0893] To a tatrehydrofuran (3 mL) solution of (4-(6-fluoro-pyridin-2-yloxymethyl)-phenyl) acatohydroximoyl chloride (200 mg. 0.6 78 mmol) described in Manufacturing Example 51-5 and 3-ethynyl-pyridin-2-ylarine (50 mg. 0.423 mmol) described in Manufacturing Example 1-2-3 was added triethylamine (237 µL, 1.7 mmol) at room temperature, which was stirred for 2 hours at 50°C. Water was added to the reaction solution at room temperature, which was three databased with ethyl aceted. The organic layer was sended with saturated aqueous sodium chloride and dried over anthydrous manufacturing and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column forhomatography (heptane : ethyl aceted = 4:1 7 = 2;1) to obtain the title compount (65 mg. 23%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 4.07(2H, s), 5.32(2H, s),5.84(2H, brs), 6.27(1 H, s), 6.47-6.50(1 H, m), 6.84-6.67 (1 H, m), 6.71-6.74(1 H, m), 7.30(2H, d, J=8.4Hz), 7.43(2H, d, J=8.4Hz), 7.63-7.69(1H, m), 7.72-7.75(1 H, m), 8.11-8.12 (1H, m).

[0694] The starting material, (4-(6-fluoro-pyridin-2-yloxymethyl)-phenyl) acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 55-1-1] 4-(6-Fluoro-pyridin-2-yloxymethyl)-benzonitrile

50 [0695]

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[0696] To an N.N-dimethylformamide (50 mL) solution of 2,6-diffuoropyridine (5 q, 43.4 mmol) and 4-(hydroxymethyl)

benzonfrile (6.67 g, 65.1 mmol) was added sodium hydride (2.56 g, 65.1 mmol, 60% in oil) at room temperature. This mixture was stirred for 4 hours at 70°C. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium suffate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH-silica gel column chromatography (heptane: ethyl acetate = 10:1 -1 -4:1) to obtain the title compound (5.99 g, 61 %).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.41 (2H, s), 6.74-6.77(1H, m), 6.87-6.89(1H, m), 7.63-7.66(2H, m), 7.85-7.88(2H, m), 7.90-7.96(1 H, m).

[Manufacturing Example 55-1-2] 4-(6-Fluoro-pyridin-2-yloxymethyl)-benzaldehyde

[0697]

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[0689] To a toluene (41 mL) solution of 4-(6-fluoro-pyridin-2-yloxymethyl)-benzontirile (5.99 g., 26.2 mmol) described in Manufacturing Example 56-1-1 was added disobutyl aluminum hydride (1.01 M toluene solution, 33.3 mmol) under nitrogen atmosphere at -70°C to -78°C. This mixture was stirred for 2 hours at room temperature. This mixture was partitioned into ethyl acetate and 20% squeous Rochelle salt solution. After removal of insoluble matter by filtrating through a Cellite bed, the filtrate was partitioned. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sultate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate =10:1-4:1) to obtain the title compound (4.57 or .75%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 5.43(2H, s), 6.50-6.53(1 H, m), 6.70-6.72(1 H, m), 7.60-7.62(2H, m), 7.66-7.72(1H, m), 7.88-7.91 (2H, m), 10.0(1H, s).

[Manufacturing Example 55-1-3] 2-Fluoro-6-(4-(E)-2-nitro-vinyl)-benzyloxy)-pyridine

[0699]

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[0700] A mixture of 4-(6-fluoro-pyridin-2yloxymethyl)-benzaldehyde (4.57 g. 18.8 mnol) described in Manufacturing Example 56-1-2, nitromethane (2.13 ml., 39.6 mmol), ammonium acetate (2.29 g. 29.7 mmol) and acetic acid (4.57 ml.) was stirred for 19 hours at 100°C. This mixture was cooled to from temperature and concentrated under a reduced pressure. The residue was dissolved in ethyl acetate, washed with water and saturated aqueous sodium chloride, dried over anyydrous magnesium suitlea, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 4:1) to obtain the title compound (3.44 g, 63%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.39(2H, s), 6.50-6.53(1 H, m), 6.68-6.71 (1 H, m), 7.52-7.61 (5H, m), 7.66-7.72(1 H, m), 8.03-8.99 (1 H, m).

[Manufacturing Example 55-1-4] 2-Fluoro-6-(4-(2-nitro-ethyl)-benzyloxy)-pyridine

[0701]

[0702] To a dimethyl sulfoxide (68.5 ml.) solution of 2-fluoro-6(4-(6)-2-nitro-winyl-benzyloxy)-pyridine (3.4-g. 1.25. mmol) described in Manufacturing Example 55-1.3 and acotic acid (2.4 ml.) was added sodum borohyridine (757 mg. 20 mmol) at room temperature while cooling appropriately. This mixture was estirred for 4 hours at room temperature. This mixture was unartification of interest the cooling appropriately. This mixture was separated, washed with saturated acuesous sodium cholinde, dired over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by slica gel column chromatography (heptane: ethyl acetate = 10: 1-4: 1) to obtain the tife compound (1.6 a. 46%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.31-3.35(2H, m), 4.60-4.63(2H, m), 5.31 (2H, s), 6.48-6.50(1H, m), 6.64-6.67(1H, m), 7.22-7.24(2H, m), 7.41-7.43(2H, m), 7.63-7.69(1 H, m).

[Manufacturing Example 55-1-5] (4-(6-Fluoro-pyridin-2-yloxymethyl)-phenyl) acetohydroximoyl chloride

20 [0703]

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[0704] To a methanol (20 mL) solution of 2-fluoro-6-(4-(2-nitro-ethyl)-benzyloxy)-pyridine (1.6 g. 5.79 mmol) described in Manufacturing Example 55-1-4 was added lithium methoxide (449 mg., 1.1.6 mmol). This mixture was stirred for 1 hour at room temperature. The mixture was concentrated under a reduced pressure, water in the residue was according to the state of the control of

(Example 56] 3-(3-4-(5-Fluoro-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0705]

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[9706] To a tetrahydrofuran (5 mL) solution of ((4-(5-fluor-opyridin-2-yloxymethyl)-phenyl)acetohydroximoyl chloride (800 mg, 2-12 mmol) described in Manufacturing example 56-1-5 and 3-ethyl-pyridin-2-ylamine (200 mg, 1.58 mm) described in Manufacturing Example 1-2-3 was added triethylamine (494 mL, 6.8 mm) at room temperature, which was stirred for 4 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous mannesium sulfate, and the solvent was everyoned under a reduced pressure. The residue was outfield by NH silica

gel column chromatography (heptane: ethyl acetate = 4:1 - 2:1) to obtain the title compound (214 mg, 21 %).
14-NMR Spectrum (CDCl₃) à (ppm): 4042H, s), 5.08(2H, s), 5.54(2H, brs), 6.27(1 H, s), 6.71-6.74(1 H, m), 7.13-7.16
(1 H, m), 7.31-7.39(6H, m), 7.71-7.73(1 H, m), 8.11-8.14(2H, m)

[0707] The starting material, (4-(5-fluoro-pyridin-2-yloxymethyl)-phenyl) acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 56-1-1] 4-(5-Fluoro-pyridin-2-yloxymethyl)-benzonitrile

[0708]

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[0708] To an N.N-dimethylformamide (50 m.l.) solution of 2-bromos-fluoropydriane (5g, 28.4 mmol) and 4-(hydroxymethyl-beacontrile, 66 f. g., 42.4 mmol, 68 f. in oil pit room in magnetizer. The mixture was affired for 3 hours at 70 f.C. The mixture was partitioned into eithyl acetate and water. The organic layer was separated, which washed with water, dired over an influorous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH-silica gel course chromotography (heptane: ethyl acetate = 61:12:11:11:11:ethyl acetate 10 obtain the title compound (5.5.0.65%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 5.15(2H, s), 7.14-7.17(1H, m), 7.39-7.41 (1H, m), 7.53-7.55(2H, m), 7.70-7.72(2H, m), 8.12-8.13(1 H, m).

[Manufacturing Example 56-1-2] 4-(5-Fluoro-pyridin-2-vloxymethyl)benzaldehyde

[0710]

[0711] To a toluene solution (37 mL) of 4.6-fluoro-pyridin-2yloxymethyl)-benzonitrile (5.5 g. 24.1 mmol) described in Manufacturing Example 56-1-1 was added dissolutyl aluminum hydride (35.8 mL, 1.01 M toluene solution, 38.2 mmol) under nitrogen atmosphere at-70°C to -78°C. This mixture was strend for 3 hours at room temperature. This mixture was partitioned into ethyl acetade and 20% aqueous Rochelle salt solution. After removal of insoluble matter by filtrating through a Cellie pad, the filtrate was partitioned. The organic layer was separated, washed with saturated aqueous soldium chloride, dried over enhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 4:1-2:1) to obtain the title compound (2.71 g. 49%).

¹H-NMR Spectrum (DMSO-d₀) δ (ppm): 5.31-5.33(2H, m), 7.46-7.50(1H, m), 7.57-7.59(1 H, m), 7.64-7.69(2H, m), 7.88-7.96(2H, m), 8.21-8.22(1 H, m), 10.0(1 H, s).

[Manufacturing Example 56-1-3] 5-Fluoro-2-(4-((E)-nitro-vinyl)-benzyloxy)-pyridine

[0712]

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[0713] A mixture of 4-(5-fluoro-pyridin-2-yloxymethyl)benzaldehyde (2.71 g, 11.7 mmol) described in Manufacturing Example 56-1-2, nitromethane (1.26 mL, 23.4 mmol), ammonium acetate (1.35 g, 17.6 mmol) and acetic acid (30 mL)

was stirred for 10 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (2.9 g).

[0714] This compound was used in the following reaction without being purified.

[Manufacturing Example 56-1-4] (5-Fluoro-2-(4-(2-nitro-ethyl)-benzyloxy)-pyridine

[0715]

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[0716] To a dimethyl sulfoxidie (49 mL) solution of 5-fluoro-2-(4-(16)-nitro-vinyl)-benzyloxyl-pyridine (2.9 g, 10.6 mmol) described in Manufacturing Example 56-13 and acquise caid (2.9 mL) was added sodium borohydride (642 mg, 17 mmol) at room temperature while cooling appropriately. This mixture was stirred for 1 hour at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with saturated aqueous sodium choride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH-silica gel column chromatography (heptane: ethyl acetate = 10:1) to obtain the title compound (1.83 a. 56%).

 1 H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.21-3.25(2H, m), 4.83-4.87(2H, m), 5.15(2H, s), 7.31 (2H, d, J=8Hz), 7.40(2H, d, J=8Hz), 7.44-7.48(1 H, m), 7.54-7.57(1 H, m), 8.18-8.19(1H, m).

[Manufacturing Example 56-1-5] (4-(5-Fluoro-pyridin-2-yloxymethyl)-phenyl) acetohydroximoyl chloride

[0717]

CI-N N

[0718] To a methanol (20 mt.) solution of (5-fluore-2-(4-(2-nitro-ethyl-benzy/oxy)-cyridine (1.63 g. 5 mmol) described in Manufacturing Example 56-1-4 was added lifthium methoxide (448 mg, 11.8 mmol). This mixture was stirred for 2 hours at room temperature. This mixture was concentrated under a reduced pressure, water in the residue was azeo-tropically distilled with toluene, and the residue was diluted with methylene chloride (24 mt.) and tetrahydrofuran (12 mt.). This was cooled to -78°C and fittainur (iv) tetrahoride (20 nm.), 18.9 mmol) was added dropwise into the suspension. This mixture was stirred for 2 hours at room temperature. This mixture was cooled to -78°C and partitioned into ethyl acetate and ice water. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was pulverized in ethyl acetate. This solid was collected and dried under a reduced pressure to obtain the title compound (1.75 g).

[0719] This compound was used in the following reaction without further purification.

[Example 57] 3-(3-(1-Benzyl-1H-pyrrol-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0720]

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10 [0721] The title compound (27 mg, 7.3%) was obtained according to the methods similar to those of Example 3 using 3 ethynyl-pridin-2 ylamine (47 mg, 0.58 mmg) described in Manufacturing Example 12-3 and (1-benzyl-1 H-pyrrol3-yl)-acetohydroximyl chloride (280 mg, 1.1 mmol) described in Manufacturing Example 57-1-3.

¹H·NMR Spectrum (DMSO-d₆) δ (ppm): 3.78 (2H, s), 5.03 (2H, s), 5.99 (1H, d, J=2.0Hz), 6.24 (2H, brs), 6.68-6.80 (4H, m), 7.18 (2H, d, J=8.4Hz), 7.23-7.36 (3H, m), 7.87 (1 H, dd, J=2.0, 8.0Hz), 8.08 (1 H, dd, J=2.0, 4.8Hz).

[0722] The starting material, (1-benzyl-1/H-pyrrol-3-yl) acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 57-1-1] 1-Benzyl-3-((E)-2-nitro-vinyl)-1 H-pyrrole

[0723]

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[0724] The title compound (3.0 g, 85%) was obtained according to the methods similar to those of Manufacturing Example 3-1-3 using 1-benzyl-1 H-pyrrole-3-carbaldehyde (2.9 g, 15 mmol).

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 5.16 (2H, s), 6.60-6.63 (1 H, m), 6.99 (1 H, dd, J=2.0, 2.0Hz), 7.22-7.40 (5H, m), 7.60 (1 H, dd, J=2.0, 2.0Hz), 7.80 (1 H, d, J=13.2Hz), 8.03 (1 H, d, J=13.2Hz).

[Manufacturing Example 57-1-2] 1-Benzyl-3-(2-nitro-ethyl)-1H-pyrrole

35 [0725]

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[0726] The title compound (2.3 g, 75%) was obtained according to the methods similar to those of Manufacturing Example 3-1-4 using the 1-benzyl-3-((E)-2-nitrovinyl)-1H-pyrrole (3.0 g, 13 mmol) described in Manufacturing Example 57-1-1.

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.00 (2H, d, J=6.8Hz), 4.67 (2H, d, J=6.8Hz), 5.01 (2H, s), 5.92 (1 H, dd, J=2.0, 2.0Hz), 6.66 (1 H, dd, J=2.0, 2.0Hz), 6.73 (1 H, dd, J=2.0, 2.0Hz), 7.13-7.17 (2H, m), 7.23-7.35 (3H, m).

[Manufacturing Example 57-1-3] (1-Benzyl-1H-pyrrol-3-yl) acetohydroximoyl chloride

[0727]

[0728] The title compound (550 mg, 51 %) was obtained according to the methods similar to those of Manufacturing Example 3-1-5 using the 1-benzyl-3-(2-nitro-ethyl)-1 H-pyrrole (280 mg, 1.1 mmol) described in Manufacturing Example 57.1-2

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.57 (2H, s), 5.03 (2H, s), 5.97 (1 H, dd, J=2.0, 2.0Hz), 6.77 (1 H, dd, J=2.0, 2.0Hz), 6.79 (1 H, dd, J=2.0, 2.0Hz), 7.15-7.22 (2H, m), 7.23-7.40 (3H, m), 11.46 (1 H, s).

[Example 58]3-(3-(6-(4-Fluoro-benzyloxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0729]

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[0730] To a tetrahydroturan (10.0 mL) solution of (6:4-flutor-benzyloxy)-pyridin-3-yl)-acetohydroximoyl chloride (150 mg, 0.508 mmol) described in Manufacturing Example 58-15 and 3-qtvny-pyridin-2-ylamine (30.0 mg, 0.284 mmol) described in Manufacturing Example 18-2-3 was added triethylamine (106 µL, 0.782 mmol) at room temperature, which was therefore the hours at 60°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chronatography (ethyl acetate: heptane = 1 × 2) to lottain the title compound (2.1 2 mg, 22.25°C).

1H-NMR Spectrum (DMSO-d₆) 6 (ppm); 4.00 (2H, s), 5.3.1 (2H, s), 6.27 (2H, brs), 6.88-6.71 (1 H, m), 6.83 (1 H, s), 6.84-6.86 (1 H, m), 7.17-7.22 (2H, m), 7.47-7.51 (2H, m), 7.67-7.70 (1 H, m), 7.66-7.88 (1H, m), 8.08-8.10 (1 H, m), 8.16-8.17 (1 H, m).

[0731] The starting material, (6-(4-fluoro-benzyloxy)-pyridin-3-yl)-acetohydroximoyl chloride; was synthesized as follows.

[Manufacturing Example 58-1-1] 5-Bromo-2-(4-fluoro-benzyloxy)-pyridine

[0732]

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[0733] To an N.N-dimethylformamide (30.0 ml.) solution of 4-fluorobenzyl alcohol (2.6 g., 2.0.6 mmol) was added sodium hydride (0.88 g., 2.2.2 mmol, 60% in oil) under nitrogen atmosphere at 0°C, which was stirred for 10 minutes at room temperature. Next, 2.5-dipromopyridine (3.5 g., 14.8 mmol) was added at 0°C, and stirred for 19 hours at room temperature. Water was added to the reaction solution at room temperature, which was then extracted with ethyl accetate. The organic layer was washed with saturated aqueues sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : heptane = 1 : 5) to obtain the title compound (3.7 g. 8, 88.9%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.29 (2H, s), 6.68-6.70 (1 H, m), 7.02 -7.06 (2H, m), 7.38-7.42 (2H, m), 7.61-7.64 (1 H, m), 8.19-8.20 (1 H, m).

[Manufacturing Example 58-1-2] 6-(4-Fluoro-benzyloxy)-pyridine-3-carbaldehyde

[0734]

[0735] To a diethyl ether (150 m.l.) solution of 5-bromo-2/4-fluoro-benzyloxy/pyridine (3.75g 13.3 mmol) described in Manufacturing Example 86-1 was added in-built hillhor (2.5 fb. m. hexame solution, 2.6 fm. l. 16.0 mmol) on a dry ice-ethanol bath (7.8°C) under nitrogen atmosphere, which was stirred for 30 minutes at 7.8°C. N.h-dimethylformamide (1.54 ml., 2.0.0 mmol) was then added dropwise and stirred for 5 minutes at 7.8°C. The resction solution was allowed to room temperature, water was added, and the solution was extracted with sthyl acotate. The organic layer was washed with saturated equeous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purifiedly sellicage olculum-chromotography (eth) locatette: heptane = 1.30 bothalm theil compound (2.38) 7.2.5%). H-NMR Spectrum (CDCL) 8 (ppmi): 5.45 (2H, s), 6.87-6.90 (1 H, m), 7.05-7.09 (2H, m), 7.42-7.46 (2H, m), 8.07-8.10 (1H, m), 8.68-6.6 (1 H, m), 9.66 (1 H, m), 9.67-8.10

[Manufacturing Example 58-1-3] 2-(4-Fluoro-benzyloxy)-5-((E)-2-nitro-vinyl)-pyridine

[0736]

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[0737] To an acetic acid (20.0 m.l.) solution of 64.4-fluor-benzyloxyl-pyridine-3-carbaldehyde (2.23 g. 9.64 mnol) described in Manufacturing Example 58-1-2 were added nitromethane (2.94 g. 48.2 mmol) and ammonium acetate (1.48 g. 19.3 mmol) under nitrogen atmosphere, which was stirred for 2.5 hours at 10°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was extracted with ethyl acetate. This organic layer was exached with water and saturated aqueous sodium-hofried, ciried over anhydrous rangesuim sulfate, and filtered. The solvent was evaporated from the filtrate under a reduced pressure to obtain the title compound (2.60 g) as a crude product. 1H-NNR Spectrum (DMSO-d₆) 5 (ppm): 5.41 (2H, 8), 7.00-7.02 (1 H, m), 7.18-7.24 (2H, m), 7.50-7.54 (2H, m), 8.14-8.18 (1 H, m), 8.26-8.26 (1 H, m), 8.64-8.66 (1 H, m). 8.64-8.67 (1 H, m), 8.64-8.67 (1 H, m), 8.64-8.67 (1 H, m), 8.7.65 (1 H, m), 8.64-8.67 (1 H, m), 8.64-8.67 (1 H, m), 8.7.65 (1 H, m), 8.7.65 (1 H, m), 8.7.65 (1 H, m), 8.7.65 (1 H, m), 8.64-8.67 (1 H, m), 8.64-8.67 (1 H, m), 8.7.65 (1 H, m), 8.64-8.67 (1 H, m), 8.64-8.67 (1 H, m), 8.7.65 (1 H, m), 8.64-8.67 (1 H, m), 8.7.65 (1 H, m), 8.

[Manufacturing Example 58-1-4] 2-(4-Fluoro-benzyloxy)-5-(2-nitro-ethyl)-pyridine

[0738]

[0738] To a dimethyl sulfoxide (20 0 m.), solution of 2:(4-fluoro-benzyloxy)-5-((6):2-nitro-vinyl)-pyridine (2.80, 9, 48 mmc) described in Manufacturing Example 58-1-3 and acetic acid (3.00 m.) was added sodium borohydride (574 mg, 15.2 mmo)) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 20 minutes. Water was then added cropwise at room temperature while cooling appropriately to quench sodium borohydride. The reaction mixture was extracted with with valve and the cromain leaver was washed with water and saturated aquaeous

sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:5) to obtain the title compound (756 m. 3.00%).

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.18 (2H, t, J=6.8Hz), 4.85 (2H, t, J=6.8Hz), 5.31 (2H, s), 6.84-6.86 (1 H, m), 7.18-7.23 (2H, m), 7.48-7.52 (2H, m), 7.68-7.70 (1 H, m), 8.07-8.08 (1H,m).

[Manufacturing Example 58-1-5] (6-(4-Fluoro-benzyloxy)-pyridin-3-yl)-acetohydroximoyl chloride

[0740]

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20 [0741] To a mehanol (20.0 ml.) solution of 2:(4-fluoro-benzylosy)-5:(2-intro-ethyl)-pyridine (785 mg. 2.84 mmol) described in Manufacturing Example 5:8-1-4 was added fithium methoxide (216 mg. 5.68 mmol) under nitrogen atmosphere at room temperature, which was stirred for 30 minutes at room temperature. The solvent was eveporated from the reaction mixture under a reduced pressure, and anhydrous dichloromethane (20.0 ml.) and anhydrous tetrahydrofuran (5.00 ml.) were added to the residue. Titanium (fv) chinoide (989 bg. 1.09 mmol) was added dropwise into the reaction mixture on a dry los-ethanol bath (78°C), which was stirred for 45 minutes at room temperature. Water, ethyl acetate and tetrahydrofuran were added to the reaction mixture on an los bath (6°C), and the organic layer was extracted with ethyl acetate. This organic layer was washed with water and saturated aqueous sodium chioride, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated from the filtrate under a reduced pressure to obtain the title compound (60 ft m. 95.7%) as a crude product.

39 1H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.79 (2H, s), 5.31 (2H, s), 6.85-6.87 (1H, m), 7.18-7.22 (2H, m), 7.48-7.52 (2H, m), 7.60-7.62 (1H, m), 8.07-8.08 (1H, m), 11.76 (1H, s).

[Manufacturing Example 59] 3-(3-(4-(4-Fluoro-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

35 [0742]

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[0743] To a tetrahydrofuran (3 mL), solution of (4-(4-fluoro-pyridin-2-ylowymethyl)-pheniyl-acetohydroximoyi chloride (200 mg), 0-679 mmo) described in Meunifacturing Example 9-1-6 and 3-ethylyl-yloydin-2-ylamine (50 mg, 0.423 mmo)) described in Menufacturing Example 1-2-3 was added triethylamine (237 µL, 1.7 mmol) at room temperature, which was stirred for 4 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was availed with saturated adjecuous sodium chloride, and riefd over anthydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate – 4.1:2-1:1) to betain the title compound (57 mg, 22%). 1H-NMR Spectrum (CDCl₃) 8 (ppm): 4.09(2H, s), 5.09(2H, s), 5.49(2H, bn), 6.30(1 H, s), 6.74-6.77(1H, m), 6.80-6.82 (1 H, m), 8.90-6.91 (1H, m), 7.37-74(2H, m), 7.76-77(H, H, m), 8.19-8.21(2H, m), 8.19-8.21(2H, m), 8.19-8.21(2H, m)

55 [0744] The starting material, (4-(4-fluoro-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride, was synthesized as follows:

[Manufacturing Example 59-1-1] 4-(4-Fluoro-pyridin-2-yloxymethyl)-benzonitrile

[0745]

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N=

[0746] To an N.N dimethylformamide (15 ml.) solution of 2-chloro-4-fluoropyridine (2.88 g. 2.1.9 mmn)) and 4-(hydroxymethylbenzonitrile (4.37 g. 32.9 mmo) was added sodium hydride (1.29 g. 32.9 mmo), 60% in oil) at room tenserature. This mixture was surried for 4 hours at 70°C. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane : ethyl acetate = 4.1 - 2.11) to ethin the filte compound (4.08 g. 82°A).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.17(2H, s), 6.81-6.83(¹H, m), 6.908-6.913(1 H, m), 7.52-7.54(2H, m),7.70-7.73 (2H, m), 8.23-8.24(1 H, m).

20 [Manufacturing Example 59-1-2] 4-(4-Fluoro-pyridin-2-yloxymethyl)-benzaldehyde

[0747]

[0748] To a toluene solution (28 mL) of 4-(4-fluore-pyridin-2y/loxymethyl-benzontifile (4.08 g, 17.9 mmol) described in Manufacturing Example 59-1-1 was added dilsochuţi aluminum hydride (26.6 mL, 1.01 M toluene solution, 26.9 mmol) under nhrogen atmosphere at -70°C to -78°C. This mixture was stirred for 3 hours at room temperature. This mixture was partitioned into ethyl accetate and 20% aqueous Rochelle salt solution. After the insoluble material had been removed by filtering through a Cellie pach, the filtrate was partitioned. This organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 4 : 1 -2 : 1) to obtain the title compound (1.5 g, 30%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.20(2H, s), 6.82-6.84(1 H, m), 6.92-6.93(1 H, m), 7.57-7.59(2H, m), 7.93-7.95(2H, m), 8.22-8.24(1 H, m), 10.0(1 H, s).

[Manufacturing Example 59-1-3] 4-Fluoro-2-(4-((E)-2-nitro-vinyl)-benzyloxy)-pyridine

[0749]

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[0750] A mixture of the 4-(4-fluoro-pyridine-2-yloxymethyl)-cenzaldehyde (1.5 g, 6.49 mmol) described in Manufacturing Example 59-1-2, nitromethane (689 µL, 13 mmol), ammonium acetate (750 mg, 9.74 mmol) and acetic acid (15 mL)) was stirred for 6 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.72 g). [0751] This compound was used in the following reaction without being purified.

1H-NMR Spectrum (CDCl₂) δ (ppm): 5.16(2H, s), 6.82-6.84(1H, m), 6.917-6.923(1H, m), 7.49-7.51 (2H, m), 7.59-7.62

(3H, m), 8.00-8.04(1 H, m), 8.23-8.24(1 H, m).

[Manufacturing Example 59-1-4] 4-Fluoro-2-(4-(2-nitro-ethyl)-benzyloxy)-pyridine

5 [0752]

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[0753] To an acatic acid (1.7 mL) and dimethyl sulfoxide (28 mL) solution of 4-fluoro-24-4((E)-2-tinto-vinyl-benzy-loxyl-pyridine (1.72 g, 8.27 mmol) described in Manufacturing Exemple 59-13 was added sodium borohydride (380 mg, 10 mmol) at room temperature while cooling appropriately. This mixture was settred for 5 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water and sextured aqueous sodium chioride, dired over enhydrous magnesium sulfate, and filtered. The filtred was concentrated under a reduced pressure, and the residue was purified by silics gel column chromatography (heptane: ethyl acetate acetate

1H-NMR Spectrum (CDCl₃) 8 (ppm): 3.33-3.37(2H, m), 4.61-4.65(2H, m), 5.09(2H, s), 6.81-6.83(1 H, m),6.91-6.92(1H, m), 7.25-7.27(3H, m),7.36-7.38(1H, m), 8.20-8.22(1H, m).

[Manufacturing Example 59-1-5] (4-(4-Fluoro-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride

[0754]

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[0755] To a methanol (12 mL) solution of 4-fluoro-2-(4-(2-nitro-ethyl)-benzyloxy)-pyridine (960 mg, 3.47 mmol) described in Manufacturing Exemple 59-1-4 was added lithium methodide (264 mg, 6.94 mmol). This mixture was stirred for 1 hour at room temperature. This mixture was concentrated under a reduced pressure, water in the residue was azeotropically distilled with toluene, and that residue was diluted with methylene chloride (14 mL), and tetrahydrofluran (72 mL). This was colled to -78°C, and titanium (19/1 betrachtoride (12 mL, 1.11 mmol) was added dropwise into the suspension. This mixture was stirred for 2 hours at room temperature. This mixture was cooled to -78°C, and partitioned into ethyl acetate and loe water. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhytrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was pulverized in ethyl acetate. This solid was collected and dried under a reduced pressure to obtain the title compound (990 mg).

[0756] This compound was used in the following reaction without further purification.

[Example 60] 3-(3-(3-(Pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylarnine

50 [0757]

[0758] To a tetrahydrofuran (3 mL) solution of 3-(pyridin-2-yimethoxy)-phenyl)-acetohydroximoyi chioride (200 mg. 0.783 mmol) described in Manufacturing Example 0-14 and 3-ethyryydridi-2-ylamine (55mg. 0.481 mmol) oscerbed in Manufacturing Example 1-2-3 was added triethylamine (252 µL, 1.81 mmol) at room temperature, which was their strength of Lours at 50°C. Water was added to the reaction mixture at room temperature, which was then attracted with ethyl acetats. The organic layer was washed with water and saturated aqueous sodium chloride and dired over anhydrous magnesium sulfate, and the solvent was everporated under a reduced pressure. The residue was purified by NH silica electromactography (hepthane: ethyl acetate = 1: 1 = 2; 1 - 1; 1) to obtain their the compound (52 mg. 20%). 1H-MMR Spectrum (CDCl₂) 3 (ppm): 4.03(2H, s), 5.20(2H, s), 5.80(2H, brs), 6.26(1H, s), 6.73-6.76(1H, m), 6.89-6.91 (4H, m), 7.19-7.56(1H, m), 7.80-7.51 (1H, m), 7.88-7.772(H, m), 8.99-8.91 (4H, m), 7.87-7.56(1H, m), 6.89-6.91

[0759] The starting material, 3-(pyridin-2-ylmethoxy)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 60-1-1] 3-(Pyridin-2-ylmethoxy)-benzaldehyde

5 [0760]

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[0761] 3-Hydroxylpenzudehytye (3 g. 24 6 mmol) and potassium carbonate (10.2 g. 73.8 mmol) were suspended in N.N-dimethyltomamide (60 ml.). 2-Picoply chiloride hydrochloride (4.44 g. 27.1 mmol) was added to this suspension, and stirred for 14 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residure was purified by slidic gel column chromotography (heptane: ethyl acetate = 4:1-2:1-1:1) to obtain the title compound (2.98 g. 57%).

H-NMR Spectrum (CDCL) is (pomis 5:2724 s.) 7.244-7.2624 h. m.), 7.71-7.76(1 H.m.), 8.62-8.63(1 H.

[Manufacturing Example 60-1-2] 2-(3-((E)-2-nitro-vinyl)-phenoxymethyl)-pyridine

[0762]

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m), 9.98(1 H, s).

[0763] A mixture of 3-(pyridin-2-yimethoxy)-benzaldehyde (2,88 g, 14 mmol) described in Mamufacturing Example 60-1-1, nitromethane (1,51 mL, 28 mmol) armonium acetate (1,82 g,21 mmol) and acetic acid (30 mL) was stirred for 6 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica get column chromatography (heptane: ethyl acetate = 4:1-2:1-1:1) to obtain the title compound (2.56 g, 17 %).

¹H-NMR Spectrum (CDCl₂) δ (ppm): 5.27(2H, s), 7.12-7.17(3H, m), 7.28-7.30(1 H, m), 7.35-7.39(1 H, m), 7.52-7.58(2H, m), 7.74-7.78(1 H, m), 7.94-7.97(1 H, m), 8.62-8.64(1 H, m).

Manufacturing Example 60-1-31 2-(3-(2-Nitro-ethyl)-phenoxymethyl)-pyridine

[0764]

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[0765] To an acetic acid (2,5 mL), and dimetrity sulfloxide (43 mL) solution of 2.54(E)2-nitro-vinyl-phenoxymetrilyl-py-didne (2.56 g, 10 mmol) described in Manufacturing Example 60-1-2 was added acidium borohydride (605 mg, 16 mmol) at room temperature while cooling appropriately. This mixture was sittered for 1.5 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dired over anhydrous magnesium sulfers, and filtered the The filtrate was concentrated under a reduced pressure, and the recibius was purified by silica gel column chromatography (heptane: ethyl acetate = 10:1-4:1-1:1) to obtain the little compound (1.68 g, 64%). 14-1MM Spectrum (DMSO-d₃) à (ppm): 3:03-23(2(1, m), 4.83-4.87(21, m), 5.44(21, s), 6.86-4.86(11, m), 8.91-6.39 (11, m), 7.647-5.0(11, m),

[Manufacturing Example 60-1-4] 3-(Pyridin-2-vlmethoxy)-phenyl)-acetohydroximovl chloride

[0766]

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[0767] To a methanol (20 mL) solution of 2/34/2-nitro-ethyl)-phenosymethyl)-pyridine (1,68 g.,6.43 mmol) described in Manufacturing Example 80-1-3 was added lithium methoxide (488 mg, 12.9 mmol). This mixture was stirred for 1 hour at room temperature. This mixture was concentrated under a reduced pressure, water in the residue was azootropically distilled with follower, and that residue was diluted with methylene chloride (24 mL) and sterahydrofuran (12 mL). This was cooled to 7-8°C, and thatim im (f) bit tenchloride (2.26 mL, 20.6 mmol) was added dropwise in the suspension. This mixture was stirred for 2 hours at room temperature. This mixture was cooled to 7-8°C, and partitioned into ethyl acetate and ice water. The organic layer was separated, washed with saturated aqueous sodium chloride, died over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.25 g).

[0768] This compound was used in the following reaction without further purification.

[Example 61]3-(3-(3-Benzyloxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0769]

[0770] To a tetrahydrofuran (3 mL) solution of (3-benzyloxy-phenyt)-acetohydroximoyl chloride (200 mg, 0.724 mmol) described in Manufacturing Example 61-14 and 3-ethynyl-pyridin-2-ylamine (55 mg, 0.482 mmol) described in Manufacturing Example 1-2-3 was added theirhylamine (252 pL, 1.81 mmol) at room temperature, which was stirred for 4 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with eithy acetate. The organic layer was weashed with water and sutrated equacues sodium chloride and dired over anhydrous magnesium sulfate, and the solvent was everporated under a reduced pressure. The residue was purified by NF silica elicitum chromotography (heptica) et solve et 1: 1: 2: 1) to obtain the fittle compound (58 mg, 22%).

14-NMRSpectrum (CDCl₂) 6 (ppm); 4.03(2H, s), 5.05(2H, s), 5.68(2H, brs), 6.24(1 H, s), 6.72-6.75(1 H, m), 6.88-6.90 (3H, m), 7.20°, 7.30H, m), 7.20°, 7.4(1 H, m), 8.18-8.12(1 H, m).

[0771] The starting material, (3-benzyloxy-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 61-1-] 3-Benzyloxy-benzaldehyde

[0772]

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 - ¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.13(2H, s), 7.24-7.25(1 H, m), 7.35-7.49(8H, m), 9.98(1 H, s).

[Manufacturing Example 61-1-2] 1 -Benzyloxy-3-((E)-2-nitro-vinyl)-benzene

45 [0774]

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[0775] A mixture of 3-benzyloxy-benzaldehyde (5.16 g, 24.3 mmol) described in Manufacturing Exemple 61-1-1, infromethane (2.16 mL, 48.6 mmol), ammonium acetate (2.81 g, 36.5 mmol) and acetic acid (60 mL) was stirred for 6 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with

ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate =4:12:11:1) to obtain the title compound (6:50 g, 89%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.11(2H, s), 7.10-7.16(3H, m), 7.35-7.45(6H, m), 7.53-7.57(1 H, m), 7.95-7.98(1 H, m).

[Manufacturing Example 61-1-3] 1-Benzyloxy-3-(2-nitro-ethyl)-benzene

[0776]

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0 [0777] To an acetic acid (5.5 mL) and dimethyl sulfoxide (94 mL) solution of 1-benzyloxy-9-((6)-2-nitro-viny)-benzene (5.5 g, 2.1.5 mmol) described in Manufacturing Example 61-1-2 was added sodium borohydride (1.3 g, 34.4 mmol) at room temperature while cooling appropriately. This mixture was stirred for 1.5 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with vater, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 10 : 1 - 4 : 1) to obtain the title compound (3.14 g, 57%). 11-1/MIR Spectrum (CDC)₃ i 5 (ppm): 3.73-2.1(2H, m), 4.83-4.86(2H, m), 5.07(2H, s), 6.84-6.86(1H, m), 6.88-6.90(1 H, m), 7.20-2(1H, Hm), 7.37-3.5(1H, m), 7.37-7.4 (2H, hm), 7.47-4.74(2H, hm).

[Manufacturing Example 61-1-4] (3-Benzyloxy-phenyl)-acetohydroximoyl chloride

[0778]

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[0779] To a methanol (40 mL) solution of 1-benzyloxy-3(2-nitro-ethyl)-benzene (3.14 g, 12.2 mmol) described in Manufacturing Example 61-1-3 was added tithium methoxide (927 mg, 24.4 mmol). This mixture was estired for 1 hour at room temperature. This mixture was concentrated under a reduced pressure, water in the residue was azeotropically distilled with toluene, and that residue was diluted with entrylene chloride (45 mL) and startarydrofuran (24 mL). This was cooled to -75°C, and thatin mix (IV) startachioride (2.55 mL, 26 mmol) was added dropvise in the suspension. This mixture was stirred for 2 hours at room temperature. This mixture was cooled to -78°C, and partitioned into ethyl acetale and ice water. The organic layer was separated, washed with saturated aqueous sodium chloride, died over antrydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.48 g).

[0780] This compound was used in the subsequent reaction without further purification.

[Example 62] 3-(3-(4-(5-Chloro-furan-2-vlmethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-vlamine

[0781]

10 [0782] To a mixture of (4-(5-chlor-duran-2-yimethyl-)-phenyl-pacetohydroximoy chloride (25 mg, 0.088 mmol) described in Manufacturing Example 62-16 and tetrahydroturan (1 ml) were added a thynyl-yighdir 2-yalmin (8.0 mg, 0.068 mmol) described in Manufacturing Example 1-2-3 and triethylamine (19 μL, 0.14 mmol) at room temperature a which was stirred for 1 hour at 55°C. The mixture was cooled to room temperature and water was added at the same temperature, followed by extraction with eithyl accetate. The organic layer was washed with saturated aqueous sodium of the same temperature, followed by extraction with eithyl accetate. The organic layer was washed with saturated aqueous sodium of the same temperature, followed by extraction with with accetate. The organic layer was washed with saturated aqueous sodium of the same sodium of the same temperature (plud promotagorphyl) (using an accetatific have mobile phase containing 0.1 % rifluoractic acid) to obtain the title compound as an crude product, and this was then purified by NH silica gel column chromatography (ethyl seatets: hectane = 1:1) to obtain the title compound (3.8 ms. 1 years).

1H-NMR Spectrum (CDCl₃) δ (ppm): 3.90 (2H, s), 4.04 (2H, s), 5.54 (2H, br s), 5.99 (1 H, td, J=0.9, 3.3Hz), 6.04 (1 H, d, J=3.1 Hz), 6.27 (1 H, s), 6.72 (1 H, dd, J=4.9, 7.7Hz), 7.19-7.25 (4H, m), 7.73 (1 H, dd, J=1.8, 7.7Hz), 8.12 (1 H, dd, J=1.8, 4.9Hz).

[0783] The starting material, (4-(5-chloro-furan-2-ylmethyl)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

25 [Manufacturing Example 62-1-11 4-((5-Chloro-furan-2-vl)-hydroxy-methyl)-benzonitrile

[0784]

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[0785] To a mixture of 4-indobenzonitinile (3.0 g, 13 mmnl) and letrahydrduran (40 mL) was added dropwise isopropyl magnesium chioride (1.2 M idelhy lether solution, 11 mL, 1.1-22 mmnl) at 7:8°C, which was stirred for 1 hour at 0°C. The reaction mixture was cooled to -78°C, 5-chloro-2-fundleshyde (2.2 g, 17 mmnl) was added at that temperature, and the temperature was gradually raised to 0°C. Following 30 minutes of string at 0°C, saturated aqueous ammonium chioride solution, water and ethyl acetate were added to extract the reaction mixture. The organic layer was washed successively with saturated aqueous sodium hydrogencarbonate solution and saturated aqueous sodium chioride, and the solvent was evaporated under a raduced pressure. Eithyl acetate was added to the residue, which was then filtered with NH slica gel. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.2 g) as a crude product. This compound was used in the subsequence to accompany was used to the propound (3.2 g) as a crude product. This compound was used in the subsequence treation without further purification.

[Manufacturing Example 62-1-2] 4-(5-Chloro-furan-2-ylmethyl)-benzylamine

[0786]

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[0787] To a mixture of lithium aluminum hydride (3.3 g, 69 mmol) and tetrahydrofuran (100 mL) was added aluminum chloride (13 g, 98 mmol) at 0°C, which was stirred for 1 hour at room temperature. A mixture of 4-(16-chloro-funn-2-vill-hydroxy-methyll-benzonithie (3.2 g) described in Manufacturing Example (5-11 and tetrahydrofuran was added

dropwise into the reaction mixture, and stirred for 1 hour at room temperature. A 28% aqueous ammonia solution was added dropwise into the reaction mixture at 0°C to quench the excess reagent. The reaction mixture was allowed to room temperature and filtered through a Cellite pad. The solvent was evaporated from the filtrate under a reduced pressure, and the residue was filtered after addition of diethyl other. The filtrate was concentrated under a reduced pressure to obtain the title compound (2.6 g) as a crude product.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.85 (2H, s), 3.90 (2H, s), 5.97 (1H, td, J=0.9, 3.1 Hz), 6.04 (1 H, d, J=3.1Hz), 7.20 (2H, d, J=8.2Hz), 7.26 (2H, d, J=7.9Hz).

[Manufacturing Example 62-1-3] (4-(5-Chloro-furan-2-ylmethyl)-phenyl)-methanol

[0788]

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[0788] To a mixture of 4-(5-chloro-furan-2-yimethyl)-benzylamihe (2.6 g) described in Manufacturing Example 62-1-2, acetic acid (25 mL) and water (25 mL) was added sodium nitrite (9.8 g, 140 mmol) at 0°C, which was stirred for 40 minutes at room temperature. Water and ethyl acetate were added to extract the reaction mixture. The organic layer was weshed successively with water, saturated sodium hydrogencerbonate and saturated acqueous sodium chloride, and the solvent was evaporated under a reduced pressure. Methanol (25 mL) was added to the residue at 10°C, followed by addition of potassium carbonate (3.3 g, 24 mmol) at the same temperature. This was stirred for 1 hour at the same emperature. Water and ethyl acetate were added to extract the reaction mixture. The organic layer was washed successively with water, saturated sodium hydrogencerbonate and saturated aqueous sodium chloride, and the organic layer was concentrated under a reduced pressure. The residue was purified by neutral silica gel column chromatography (ethyl acetate releptane 1 - 1; 20 to boths in the title compound (1.2 mg, 44%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.91 (2H, s), 4.68 (2H, s), 5.97 (1H, d, J=3.1Hz), 6.04 (1 H, d, J=3.1 Hz), 7.23 (2H, d, J=8.1 Hz), 7.32 (2H,

[Manufacturing Example 62-1-4] 4-(5-Chloro-furan-2-ylmethyl)-benzaldehyde

[0790]

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[0791] To a mixture of (4-(5-chloro-furan-2-ymethyl)-phenyl)-methanol (650 mg, 2.9 mmol) desoribed in Manufacturing Example 62-1-3 and dichloromethane (20 mL) was added manganese dioxide (6.5 g, 75 mmol) at room temperature, which was stirred overnight at room temperature. The reaction mixture was filtered through a Celite pad. The filtrate was evaporated under a reduced pressure to obtain the title compound (550 mg, 83%).

 $\begin{tabular}{ll} $H-NMR Spectrum (CDCl_3) \delta (ppm): 4.00 (2H, s), 6.04-6.05 (1H, m), 6.07-6.08 (1H, m), 7.40 (2H, d, J=7.9Hz), 7.84 (2H, d, J=7.9Hz), 10.00 (1H, s). \\ \end{tabular}$

[Manufacturing Example 62-1-5] 2-Chloro-5-(4-(2-nitro-ethyl)-benzyl)-furan

[0792]

[0783] To a mixture of 4-(5-chloro-furar-2-yimethyl)-benzaldelhyde (270 mg, 1.2 mmol) described in Manufacturing Example 82-1.4 and acetic acid (3 ml.) were added nitromethane (800 µL, 9.3 mmol) and ammonium acutate (280 mg, 3.7 mmol) at room temperature, which was stirred for 3 hours at 100°C. The reaction mixture was cooled to room temperature, and extracted by addition of water and telly ticetate. This organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and was concentrated under a reduced pressure. To a mixture of acetic acid (0.5 ml.) and dimethyl sulfoxide (10 ml.) was added sodium borohydride (76 mg, 2.0 mmol) at room temperature while cooling appropriately, which was stirred for 10 minutes at room temperature. Water was added to the reaction solution at room temperature, which was stirred for 10 minutes at room temperature. Water was added to the reaction solution at room temperature, which was stirred for 10 minutes at roro temperature was washed with saturated aqueous sodium chloride. The organic layer was concentrated under a reduced pressure, and the residue was purified by neutral silica gel column chromatography (ethyl acetate : heptane = 1 ; 5) to obtain the title compound (210 ms. 62%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.30 (2H, t, J=7.4Hz), 3.89 (2H, s), 4.60 (2H, t, J=7.4Hz), 5.97 (1H, d, J=3.1 Hz), 6.04 (1H, d, J=3.1 Hz), 7.15 (2H, d, J=8.2Hz), 7.19 (2H, d, J=8.2Hz).

[Manufacturing Example 62-1-6] (4-(5-Chloro-furan-2-ylmethyl)-phenyl)-acetohydroximoyl chloride

[0794]

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10785]. To a mixture of 2-chloro-5-(4-(2-nline-althyli-benzy)fluran (100 mg, 0.38 mmo) described in Manufaculting Example 62-1-8 and methanol (2 mL) was added lithium methoxide (29 mg, 0.75 mmo) at room temperature, which was stirred for 10 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure. Titanium (IV)-chloride (9 mL, 0.85 mmo) was added at -78°C to a mixture of the resulting residue, methylene chloride (2 mL, 0.94 and tetrahydrouran (1 mL), and atterned for 1 hour at 10°C. The reaction mixture was colde to -78°C, water (1 mL) was added, and the temperature was gradually raised to room temperature. Ethyl acetate and water were added to extract the reaction mixture. The organic layer was washed with water until the Pid became roughly 6. The organic layer was washed with saturated aqueous sodium chioride, and dried over anhydrous magnesium sulfate. The organic layer was concentrated under a reduced pressure to obtain the title compound (110 mg, a45%).

 1 H-NMR Spectrum (CDCl₃) δ (ppm): 3.78 (2H, s), 3.91 (2H, s), 5.97-5.99 (1 H, m), 6.04 (1 H, d, J=3.3Hz), 7.21 (4H, d, J=1.7Hz).

[Example 63]3-(3-(4-(5-Chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

40 [0796]

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[0797] Tefrahydrofuran (3 mL) and a S N aqueous sodium hydroxide solution (22 4 µL, 0.11 mmol) were acided to 4-(5(2-amine pyrdine-3-y)-isoscole-3-yimethyly-pheni (30 mg, 0.11 mmol) described in Manufacturing Example 5-1-1, which was dissolved by irradiating ultrasonic wave for 1 minute. The reaction solution was then concentrated under a reduced pressure to obtain a white solid. An N.N-dimethylformamide (1 mL) solution of 5-chloro-2-chloromethyl-yidrine (20 mg, 0.12 mmol) described in Manufacturing Example 63-1-2 was added to a suspension of this solid and N.N-dimethylformamide (1 mL), and stirred for 1 hour at 60°C. This mixture was cooled to room temperature and partitioned into water and ethyl acetale. The organic laver was separated, washed with saturated acqueus sodium

chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the resulting residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 1: 1) to obtain the title compound (41.1 nn. 29%).

¹H-NMR Spectrum (DMSO-d_b) δ (ppm): 3.97 (2H, s), 5.17 (2H, s), 6.26 (2H, brs), 6.88-6.72 (1 H, m), 6.80 (1 H, s), 6.99 (2H, d, J=8.4Hz), 7.52 (1H, d, J=8.4Hz), 7.57 (1 H, dd, J=1.6, 8.0Hz), 7.97 (1 H, dd, J=2.4, 8.4Hz), 8.09 (1 H, d, J=1.6, 4.8Hz), 8.64 (1 H, d, J=2.4Hz).

[0798] The starting material, 5-chloro-2-chloromethyl-pyridine, was synthesized as follows.

[Manufacturing Example 63-1-1] (5-Chloro-pyridin-2-yl)-methanol

[07991

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20 [0800] To a mixture of 2-bromo-5-choropyridine (2.0 g, 1.0.4 mmol) and toluene (50 mi) was acided a 1.6 M n-buty lithium hexane solution (7.8 mL, 12.5 mmol) at -78°C, which was stirred for 1 how. N-dimethyloremarible (4.0 mL, 52.0 mmol) was then acided dropwise into the mixture at the same temperature, which was then strired for a further 15 minutes at room temperature. Water and tetrahydrofuran were acided to this reaction solution, followed by vigorous striring. The organic layer was separated, washed with water and satturated queues sodium chloride, dired over arrhydrofuran strired for 1 hour at room temperature. This reaction solution was partitioned into water and tetrahydrofuran. The organic layer was separated, washed with saturated aqueous sodium chloride, dired over anhydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure, and the resulting residue was purified by NH silica gel column chromatornaby (Nexane: clidithy ether = 121 to obtain the title compound (706 mc, 47%).

³⁹ ¹H-NMR Spectrum (CDCl₃) δ (ppm): 4.75(2H, s), 7.25(1 H, dd, J=0.8, 8.4Hz), 7.68(1H, dd, J=2.4, 8.4Hz), 8.53(1 H, d, J=2.4Hz).

[Manufacturing Example 63-1-2] 5-Chloro-2-chloromethyl-pyridine

35 [0801]

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[0802] To a mixture of (6-chloro-pyridine-2-yl)-methanol (706 mg, 4.92 mmol) described in Manufacturing Example 63-1-1 and dichloromethane (70 mL) was added thionyl chloride (539 µL, 7.88 mmol), which was stirred for 1 hour own temperature. Saturated aqueous sodium hydrogenerabnate solution was added to the reaction mixture, which was then extracted with dichloromethane. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous mappesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (6200 mg, 78%).

¹H-NMR Spectrum (CDCt₃) δ (ppm): 4.66 (2H, s), 7.45 (1 H, d, J=8.0Hz), 7.71 (1 H, dd, J=2.8, 8.0Hz), 8.54 (1 H, d, J=2.8Hz).

[Example 64] 3-(3-(3-Phenoxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0803]

- 10 [0041] To a tetrallyriorturan (10.0 ml.) solution of (3-phenoxy-phenyl)-accidorydroxmoytchioride (150 mg. 0.573 mnot) described in Manufacturing Example 64-13 and 3-ethynyl-pyridin 2-ylamine (30.0 mg. 0.254 mmot) described in Manufacturing Example 11-23 was added the thysimine (106 µL, 0.762 mmot) at room temperature, which was stirred for 2 hours at 60°C. Water was added to the reaction solution at room temperature, which was then extracted with eithyl scelate. The organic layer was washed with saturated aqueous sodium chloride and fined over anthyrous magnesium of the control of the control
- ¹H-NMR Spectrum (CD₃OD) ô (ppm): 4.08 (2H, s), 6.81 (1 H, s), 6.85-6.87 (1 H, m), 6.96-6.98 (3H, m), 7.03-7.12 (3H, m), 7.29-7.36 (3H, m), 8.03-8.04 (1 H, m), 8.32-8.34 (1H, m).

[0805] The starting material, (3-phenoxy-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 64-1-1] 1-((E)-2-nitro-vinyl)-3-phenoxy-benzene

[0806]

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- 35 [0807] To an acetic acid (20.0 mL) solution of 3-phenoxyberzaldehyde (3.00 g, 15.1 mmol) were added nitromethane (4.61 g, 75.5 mmol) and ammonium acetate (2.33 g, 30.2 mmol) under nitrogen atmosphere at room temperature, which was attired for 3 hours at 100°C. Water and attyle acetate were added to the reaction mixture, and the organic layer was extracted with ethyl acetata. The organic layer was extracted with ethyl acetata. The organic layer was washed with saturated aqueous sodium chloride, diried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.60 o) as a crude product.
- ¹H-NMR Spectrum (DMSO-d_e) δ (ppm): 7.03-7.06 (2H, m), 7.12-7.19 (2H, m), 7.39-7.44 (2H, m), 7.47-7.51 (1 H, m), 7.61-7.66 (2H, m), 8.13 (1 H, d, J=13.6Hz), 8.25 (1 H, d, J=13.6Hz).

[Manufacturing Example 64-1-2] 1-(2-Nitro-ethyl)-3-phenoxy-benzen

[0808]

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50 [0099] To a dimethyl sulfoxide (30.0 mL) solution of 1-((E)-2-nitro-vinyl)-3-phenoxybenzzene (3.60 g, 1.4 9 mmol) described in Manufacturing Example 64-1-1 and cascle acid (30.0 mL) was added sodium broshydride (902 mg, 2.3 8 mmol) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 3 minutes. Water was then added drowsie at room temperature while cooling appropriately cooling appropriately. The research on mixture was extracted with eithyl.

acetate, and the organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduce pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:5) to obtain the title compound (2.47 g. 68.1%). H-NMR Spectrum (DMSO-d₄) 8 (ppm): 3.22 (2H, I, J=6.8H₂), 4.84 (2H, I, J=6.8H₂), 6.85-6.88 (1 H, m), 6.98-7.00 (3H, m), 7.04-7.06 (1, H, m), 7.127-7.61 (1 H, m), 7.127-7.61 (1 H, m), 7.127-7.61

[Manufacturing Example 64-1-3] (3-Phenoxy-phenyl)-acetohydroximoyl chloride

[0810]

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[0811] To a methanol (100 mL) solution of 1-(2-nitro-ethyl-3-phenoxy-benzene (800 mg, 3, 20 mmo) described in Manufacturing Exemple 84-1-2 was added lithium methodide (250 mg, 6.58 mmo) under nitrogen atmosphere at room temperature, which was stirred for 30 minutes at room temperature. The solvent was evergorated from the reaction mixture under a reduced pressure, and anhydrous dichioromethane (200 mL) and anhydrous tetrahydrofuran (10.0 mL) were added to the reaction mixture on a dry lose ethanol bath (-78°C), and then stirred for 45 minutes at room temperature. Water and ethyl ocetate were added to the reaction mixture on in the bath (10°C), and then stirred for 45 minutes at room temperature. Water and ethyl ocetate were added to the reaction mixture on an loe bath (10°C), and the organic layer was extracted with ethyl aceistat. The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated to obtain the title compount (860 mg, 100%) as a crude product.

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.81 (2H, s), 6.90-6.91 (2H, m), 7.00-7.04 (3H, m), 7.13-7.17 (1 H, m), 7.34-7.42 (3H, m), 11.75 (1 H, s).

[Example 65] 3-(3-(3-Butoxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0812]

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[0813] To a tetrahydrofuran (3 mJ) solution of (3-butoxy-phenyl)-acetohydroximoy chloride (150 mg, 0.621 mmo)) described in Marufacturing Example 65-14 and 3-btyphy-physine-2-yamine (4.7 mg, 0.936 mmo)l described in Marufacturing Example 1-2-3 was added triethylamine (218 µL, 1.55 mmol) at room temperature, which was stirred for 2 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with exactate. The organic layer was weakled with water and sutrated aqueous sodium chloride, and dried over annydrous magnesium sulfate. The solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 1:1 - 2:1) to obtain the title compound (33 mg, 8%).

1H-NMR Spectrum (CDCL₃) δ (ppm); 0.8-0.98(9H, m), 1.46-1.51 (2H, m), 1.72-1.79(2H, m), 3.93-3.96(2H, m), 4.02(2H, s), 5.51 (2H, brs), 6.27(1 H, s), 6.70-6.73(1 H, m), 6.79-6.86(4H, m), 7.71-7.73(1 H, m), 8.12-8.13(1 H, m), (0.141) The starting material, (3-butoxy-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 65-1-1] 3-Butoxy-benzaldehyde

[0815]

[0816] 3-Hydroxyberzaldehyde (§ 3, 24.6 mmol) and potassium carbonate (10.2 g., 73.8 mmol) were suspended in 9 N,N-dimethyltomamide (60 mt.). 1-Bromobulane (3.17 mt., 29.5 mmol) was added to this suspension and stirred for 19 hours at room temperature. This mixture was partitioned into ethyl acotate and water. This organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (4.23 g.).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 0.97-1.01(3H, m), 1.48-1.56(2H, m), 1.76-1.81 (2H, m), 4.01-4.04(2H, m), 7.16-7.19 (1H, m), 7.384-7.390(1 H, m), 7.43-7.45(2H, m), 9.97(1H, s).

[Manufacturing Example 65-1-2] 1-Butoxy-3-((E)-2-nitro-vinyl)-benzene

[0817]

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[0818] Amixture of 3-butory-benzaldehyde (4.23 g.23.7 mmol) described in Manufacturing Exemple 65-1-1, nicromethane (2.55 mL, 47.7 mmol), ammonium acetate (2.74 g. 3.5.6 mmol) and acetic acid (40 mL) was stirred for 5 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with eithy acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sufface, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by slics gel column chromatography (heptane: eithyl acetate = 41 1 - 11) to obtain the title compound (3.9 g. g. 75%). H-NMR Spectrum (DMSO-dg.) & (pmp): 0.93-0.96(3H, m), 1.42-1.47(2H, m), 1.68-1.75(2H, m), 3.97-4.05(2H, m), 7.07-7.101 H, m), 7.35-7.41 (2H, m), 7.459-7.49(2H, m), 8.09(1H, d. J.=13.6 H, b. 3.27(H, d. J.=13.6 Hz).

[Manufacturing Example 65-1-3] 1-Butoxy-3-(2-nitro-ethyl)-benzene

40 [0819]

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[0820] To an acetic acid (3.9 mL) and dimethyl sulfoxide (67 mL) solution of 1-butoxy-3-((6)-2-nitro-vinyl)-benzene (3.92 g, 17.7 mmo) described in Manufacturing Example 65-1-2 was added sodium borotydride (1.07 g, 28.3 mmo)) at room temperature while cooling appropriately. This mixture was stirred for 4 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a roduced pressure, and the residue was purified by silica get column chromatography (heptane: ethyl acetate = 10:1) to obtain the title compound (2.29 g, 58%). 1H-NMR Spectrum (CDCQ), 8 (ppm): 0.91-0.95(3H, m), 1.38-1.47(2H, m), 1.65-1.70(2H, m), 3.16-3.20(2H, m), 3.92-3.95 (2H, m), 4.82-86(2H, m), 6.86 (3H, m), 1.78-7.22(1H, m).

[Manufacturing Example 65-1-4] (3-Butoxy-phenyl)-acetohydroximoyl chloride

[0821]

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[0822] To a methanol (28 mL) solution of 1-butoxy-3-(2-nitro-ethyl-benzene (2.29 g. 10.3 mmol) described in Manutacturing Example 65-13 was added lithium methods (782 mg. 20 8 mmol). This mixture was streaf of 1-brout at room temperature. The mixture was concentrated under a reduced pressure, water in the recidue was azeotropically distilled with toluene, and that residue was distilled with methylene chioride (35 mL) and tetrahydrofuran (16.5 mL). This was cooled to 7-8°C, and ittainium (IV) tetrachioride (2.49 mL, 2.27 mmol) was added dropwise into the suspension. This mixture was etirred for 2 hours at room temperature. This mixture was cooled to 7-8°C, and partitioned into ethyl acetata and ice water. The organic layer was separated, washed with saturated aqueues sodium-chioride, difed over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound 2.85 of. This compound was used in the following reaction without further purification.

[Example 66] 3-(3-(3-Cyclopropylmethoxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

25 [0823]

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NH₂

[0824] To a tetrahydrofuran (3 m.), solution of (3-cyclopropylmethoxy-phenyl-sectohydroximoyl chloride (150 mg. 0.0624 mmorl) described in Manufacturing Example 60-14-4 and 3-ethynyl-pyridin-2-ylamine (47 mg. 0.398 mmorl) described in Manufacturing Example 1-2-3 was added triethylamine (220 µL, 1.56 mmol) at room temperature, which was stirred for 2 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl scetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magneaium sulfate. The solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 4:1 - 2:1) to obtain the title compound (26 mg. 13%).

14-NMN Spectrum (CDCL) is (como 3.23-0.862/H, m.), 0.82-0.662/H, m.), 1.24-1.261/H, m.), 376-3.80(24; m.), 4.02/2H, m

s), 5.55(2H, brs), 6.27(1 H, s), 6.70-6.74(1 H, m), 6.79-6.87(3H, m), 7.22-7.24(1 H, m), 7.71-7.74(1 H, m), 8.11-8.13 (1H, m).

(1H, m).

(1825) The starting material, (3-cyclopropylmethoxy-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 66-1-1] 3-Cyclopropylmethoxy-benzaldehyde

0 [0826]

[0827] 3-Hydroxybenzaldehyde (3 g. 2.4 6 mmol) and potassium carbonate (10.2 g. 73.8 mmol) were suspended in Ny-dimethylformamide (60 ml.), Cyclopropyl methyl chloride (2.86 ml., 29.5 mmol) was added to this suspension, and stirred for 19 hours at room temperature. This mixture was partitioned into ethyl acotate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (4.32 m).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 0.36-0.39(2H, m), 0.65-0.69(2H, m), 1.24-1.29(1H, m), 3.86-3.88(2H, m), 7.18-7.21 (1H, m), 7.37-7.38(1H, m), 7.44-7.45(2H, m), 9.97(1H, s).

[Manufacturing Example 66-1-2] 1-Cyclopropylmethoxy-3-((E)-2-nitro-vinyl)-benzene

[0828]

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20 [0829] A mixture of 3-cyclopropy/methoxy-benzaldehyele (4,32 g, 24.5 mmol) described in Manufacturing Example 66-1-1, nitromethane (2.64 mL, 49 mmol), ammonium accetate (2.83 g, 38.8 mmol) and acetic acid (40 mL) was stirred for 5 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with ethylacetate. The organic layer-was washedwith water and saturated aqueous sodium chloride, difed over anhydrous magnesium sulfate, and filter. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 4: 1 - 1: 1) to obtain the title compound (3.73 g, 69%). 'H-NMR Spectrum (DMSO-dg) 5 (pm): 0.31-0.36(24, m), 0.56-0.61 (2H, m), 1.22-1.26(1 H, m), 3.68-3.91 (2H, m), 7.09-7.11 (H, M, T, 357-41 (2H, m), 7.45-7.11 H, M, 1.347-41 H, m), 8.06-3.91 (2H, m), 7.09-7.11 (H, M, T, 357-41 (2H, m), 7.45-7.11 H, M, 1.447-41 H, m), 8.06-3.91 (2H, m), 7.09-7.11 (H, M, T, 357-41 (2H, m), 7.45-7.11 H, M, 1.447-41 H, m), 8.06-3.91 (2H, m), 7.09-7.11 (H, M, T, 357-41 (2H, m), 7.45-7.11 (4, M, T, 357-41 (4, M, M, 7.45-74 (4H, M, M, 804-41 H, M, 8.041 H, M,

[Manufacturing Example 66-1-3] 1-Cyclopropylmethoxy-3-(2-nitro-ethyl)-benzene

[0830]

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40 [0831] To an acetic acid (3.7 mL) and dimethyl sulfoxide (63 mL) solution of 1-cycloproxymethoxys-1(cf)-2-nitro-viryly-hearnea (3.75 g, 17 mmol) described in Manufacturing Example 68-1-2 was acided sodium bondyrdide (10.3), 27.2 mmol) at room temperature while cooling appropriately. This mixture was stirred for 4 hours at room temperature. That mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over analyticous rangeseisum suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue 45 was purified by silica gel column chromatography (heptane: ethyl scetate = 10:1) to obtain the title compound (2.21 g, 59%).

¹H-NMR Spectrum (DMSO-d₅)8 (ppm): 0.30-0.32(2H, m), 0.54-0.57(2H, m), 1.17-1.24(1H, m), 3.17-3.19(2H, m), 3.76-3.80(2H, m), 4.82-4.85(2H, m), 6.77-6.82(2H, m), 6.85-6.86(1H, m), 7.17-7.21(1H, m).

50 [Manufacturing Example 66-1-4] (3-Cyclopropylmethoxy-phenyl)-acetohydroximoyl chloride

[0832]

[0833] To a methanol (27 mL) solution of 1-cyclopropythenthoxy 3-(2-nitro-ethyl)-benzane (2.21 g. 10 mmol) described in Manufacturing Example (6.1-5) awas added lithium methoxide (750 mg, 20 mmol). This mixture was stirred for 1 hour at room temperature. The mixture was concentrated under a reduced pressure, water in the residie was azectropically distilled with toluene, and that residue was diluted with methylene chloride (32 mL) and tetrahydrofuran (16 mL). This was cooled to 7-8°C, and titanium (IV) tetrachioride (2-42 mL, 22 mmol) was added dropvise into the suspension. This mixture was sciented for 2 hours at room temperature. The mixture was cooled to 7-8°C and partitioned into thyl acetate and loe water. The organic layer was separated, washed with saturated equeues sodium chioride, died over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (2.5-0). This compound was used in the following reaction without further purification.

[Example 67] 3-(3-(4-Butoxy-henzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0834]

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[0835] To a terahydrofuran (3 ml, solution of (4-butovy-phenyl)-acetohydroximoyl chloride, (150 mg, 0.619 mmo) described in Manufacturing Example 67-14 and 3-ethynyl-pyridin-2-ylamine (47 mg, 0.395 mmo)) described in Manufacturing Example 12-3 was added triethylamine (216 µL, 1.55 mmo)) at room temperature, which was stirred for 2 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was devaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 4:1 + 2:1) to obtain the title compound (27 mg, 14%).

H-HMRR Spectrum (COCL) & Gommi): 0.96-0.99(31; m.), 144-15.3(21; m.), 172-17.7(21; m.), 3.93-3.96(21; m.), 4.00(2H,

s), 5.85(2H, brs), 6.25(1H, s), 6.71-6.74(1H, m), 6.86-6.88(2H, m), 7.17-7.20(2H, m), 7.72-7.75(1H, m), 8.10-8.12(1H, m). [0836] The starting material, (4-butoxy-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 67-1-1] 4-Butoxy-benzaldehyde

[0837]

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[0838] 4-Hydroxybernzidehyde (3 g. 24.6 mmol) and potassium carbonate (10.2 g, 73.8 mmol) were suspended in Ny-dimethylformamide (60 ml.). 1-Bromobutane (3.17 ml., 29.5 mmol) was added to this suspension, and stirred for 17 hours at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (4.72 o).

1H-NMR Spectrum (CDCl₃)δ (ppm): 0.97-1.01 (3H, m), 1.48-1.54 (2H, m), 1.79-1.82 (2H, m), 4.03-4.07 (2H, m), 6.98-7.00 (2H, m), 7.82-7.84 (2H, m), 9.88 (1 H, s).

[Manufacturing Example 67-1-2] 1-Butoxy-4-((E)-2-nitro-vinyl)-benzene

[0839]

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of the

[0840] Amixture of 4-butoxy-benzaldehyde (4.72 g, 28.5 mmol) described in Manufacturing Exemple 67-1-1, nitromethane (2.85 ml., 53 mmol), ammonium acetate (3.06 g, 3.85 mmol) and acetic acid (40 ml.) was stirred for 13 hours at 10°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and dittlerd with eithy acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium aulitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate 4.1:1-1:1) to obtain the title compound (4.44 g, 78°s.) H-NMR Spectrum (DMSO-d₂) 5 (ppm): 0.92-0.95 (3H, m), 1.41-1.46 (2H, m), 1.67-1.74 (2H, m), 4.04-4.09 (2H, m), 7.13 (2H, 4.3-8.8Hz), 7.82 (2H, d, 3-8.8Hz), 8.00 (9H, d, 3-8.18 Hz), 8.10 (H, d, 3-18.3 Hz), 8.10 (H, d, 3-18.4 Hz)

[Manufacturing Example 67-1-3] 1-Butoxy-4-(2-nitro-ethyl)-benzene

[0841]

[0842] To an acetic acid (4.4 mL) and dimethyl sulfoxide (75 mL) solution of 1-butoxy-4r((6)-2-nitro-vinyl-)-benzene (4.44 g, 20.1 mmol) described in Manufacturing Example 67-1-2 was added sodium borohydride (1.22 g, 32.2 mmol) at room temperature while cooling appropriately. This mixture was stimed for 4 hours at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with vater, dried over anhydrous magnesium suiteta, and filterof. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 10:1) to obtain the title compound (3.42 g, 76%). HH-NMR Spectrum (CDCI)-j\(\beta\)(pm)? 0.90-0.95 (3H, m), 1.37-1.47(2H, m), 1.63-1.70 (2H, m), 3.12-3.16 (2H, m), 3.91-3.94 (2H, m), 4.76-80 (2H, m), 6.83-6.87 (2H, m), 7.14-71.8 (2H, m), 4.76-80 (2H, m), 6.83-8.87 (2H, m), 7.14-71.8 (2H, m), 4.76-80 (2H, m), 6.83-88 (2H, m), 7.14-71.8 (2H, m), 4.76-80 (2H, m), 6.83-88 (2H, m), 7.14-71.8 (2H, m), 7.86-80 (2H, m),

40 [Manufacturing Example 67-1-4] (4-Butoxy-phenyl)-acetohydroximoyl chloride

[0843]

[0844] To a methanol (42 mL) solution of 1-butoxy-4-(2-nitro-ethyl-benzene (3.42 g. 15.3 mmol) described in Manufacturing Example 67-13 was added thinum methods (1.16 g. 9.08 mmol). This inclusive was circurd for 1 hour at room temperature. The mixture was concentrated under a reduced pressure, water in the residue was accrotopically distilled with toluene, and that residue was fausted under a reduced pressure, water in the residue was accrotopically distilled with reducene, and that residue was fausted under a reduced pressure, water in the residue was accrotopically distilled with reducene, and that residue was colored to 7-8°C, and titanium (IV) tetrachbride (3.7 mL, 3.37 mmol) was added dropwise into the suspension. This mixture was stirred for 2 hours at room temperature. This mixture was cooled to 7-8°C, and partitioned into ethyl accetate and ide water. The organic layer was separated, washed with saturated aqueous sodium chloride, diried over antifyrious magnesium suffate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.5 g). This compound was used in the following reaction without further purification.

[Example 68] 3-(3-(4-Benzylamino-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0845]

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[0846] To a tetrahydrofuran (3 mL) solution of (4-benzylamino-phenyl)-acetohydroximoyl chloride (150 mg, 0.546 mmol) described in Manufacturing Example 68-1-4 and 3-ethynyl-pyridin-2-ylamine (41 mg, 0.348 mmol) described in Manufacturing Example 1-2-3 was added triethylamine (190 μL, 1.37 mmol) at room temperature, which was stirred for 7 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 4:1 - 2:1) to obtain the title compound (14 mg, 7%). 1H-NMR Spectrum (CDCl₂) δ (ppm): 3.94 (2H, s), 4.32 (2H, s), 5.69 (2H, brs), 6.26 (1 H, s), 6.59-6.62 (2H, m), 6.71-6.74 (1 H, m), 7.06-7.09 (2H, m), 7.24-7.38 (4H, m), 7.73-7.75 (1 H, m), 8.09-8.10 (1 H, m).

(it was not observed that the proton on the amino group of NH-CH2Ph appeared on the NMR chart.)

[0847] The starting material, (4-benzylamino-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 68-1-1] 4-Benzylamino-benzaldehyde

[0848]

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[0849] To a toluene (35 mL) solution of 4-benzylamino-benzonitrile (5 g, 24 mmol) was added diisobutyl aluminum hydride (35.6 mL, 1.01 M toluene solution, 36 mmol) under nitrogen atmosphere at -70°C to -78°C. This mixture was stirred for 5 hours at room temperature. The mixture was partitioned into ethyl acetate and 20% aqueous Rochelle salt solution. After removal of insoluble matter by filtering through a Celite pad, the filtrate was partitioned. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (5 g, 99%). This compound was used in the following reaction without further purification.

[Manufacturing Example 68-1-2] Benzyl-(4-((E)-2-nitro-vinyl)-phenyl)-amine

[0850]

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[0851] A mixture of 4-benzylamino-benzaldehyde (5 g, 23.7 mmol) described in Manufacturing Example 68-1-1, nitromethane (2.55 mL, 47.7 mmol), ammonium acetate (2.74 g, 35.6 mmol) and acetic acid (50 mL) was stirred for 6 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium

sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (5.82 g).

14-NMR Spectrum (CDCl₃) & (ppm): 4.41-4.43 (2H, m), 4.68 (1 H, brs), 6.62-6.67 (2H, m), 7.25-7.39 (6H, m), 7.47-7.50
(1 H, m), 7.89-7.11 (H, m), 7.89-7.96 (1 H, m).

5 [Manufacturing Example 68-1-3] Benzyl-(4-(2-nitro-ethyl)-phenyl)-amine

[0852]

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[0.82], 2.2.9 mmol) described in Manufacturing Example 68-1.2 was added adouth borohydride (1.3 g. 3, 6.8 mmol) at room temperature while cooling approprietally. This mixture was stirred for 1 hour at room temperature. The mixture was partitioned into eithyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous amgresiums uslike, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica get column chromatography (heptane: etnly acetate = 4 : 1 - 2 : 1) to obtain the title compound (2.79 g., 48%). 11-1MR Spectrum (CDCl₂) à (ppm): 3.19-3.22 (2H, m), 4.32 (2H, s), 4.52-4.56 (3H, m), 6.60-6.62 (2H, m), 7.00-7.02 (2H, m), 2.73.73 (H, m).

25 [Manufacturing Example 68-1-4] (4-Benzylamino-phenyl)-acetohydroximoyl chloride

[0854]

[0655] To a mehanol (12 m.), solution of benzyl-(4-(2-nitro-ethyl-)phenyl-)amine (1 g. 3.91 mmol) described in Manutacturing Example 88-1-3 was added lithium methoxide (227 mg. 3.08 mmol). This mixture was stirred for 1 hour at
room temperature. The mixture was concentrated under a reduced pressure, water in the residue was a zeatropically
distilled with toluene, and that residue was diluted with methylene chloride (15 ml.) and tetrahydrofuran (7.6 ml.). This
was cooled to -78°C, and thatinium (V) tetrachloride (946 μl., 8.6 mmol) was added dropvides into the suspension. This
mixture was stirred for 1 hour at room temperature. This mixture was cooled to 7-8°C, and partitioned into ethyl acetate
and (se water. The organic layer was separated, washed with saturated aqueues sodium chloride, effod ever antydrous
grangesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound
(1,1,9). This compound was used in the following reaction without further purifications.

[Example 69] 3-(3-(4-Phenylamino-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0856]

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[0857] To a tetrahydrofuran (3 mL) solution of (4-phenylamino-phenyl)-acetohydroximoyl chloride (150 mg, 0.576 mmol) described in Manufacturing Example 69-1-4 and 3-ethynyl-pyridin-2-ylamine (43 mg; 0.367 mmol) described in Manufacturing Example 1-2-3 was added triethylamine (201 u.L. 1.44 mmol) at room temperature, which was stirred for 7 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane : ethyl acetate = 4 : 1 - 2 : 1) to obtain the title compound (48 mg, 24%). 1H-NMR Spectrum (CDCI₂) δ (ppm): 4.00 (2H, s), 5.58 (2H, brs), 5.70 (1 H, brs), 6.29 (1H, s), 6.71-6.74 (1H, m), 6.91-6.95

(1H, m), 7.03-7.07 (4H, m), 7.16-7.19 (2H, m), 7.24-7.28 (2H, m), 7.73-7.75 (1 H, m), 8.11-8.13 (1H, m),

[0858] The starting material, (4-phenylamino-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 69-1-1] 4-Phenylamino-benzaldehyde

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[0860] To a toluene (20 mL) solution of 4-phenylamino-benzonitrile (3 g, 15.4 mmol) was added diisobutyl aluminum hydride (22.9 mL, 1.01 M toluene solution, 23.1 mmol) under nitrogen atmosphere at-78°C. This mixture was stirred for 5 hours at room temperature. The mixture was partitioned into ethyl acetate and 20% aqueous Rochelle sait solution. After removal of insoluble matter by filtering through a Celite pad, the filtrate was partitioned. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3 g, 98%). This compound was used in the following reaction without further purification.

[Manufacturing Example 69-1-2] (4-((E)-2-nitro-vinyl)-phenyl)-phenyl-amine

[0861]

[0862] A mixture of 4-phenylamino-benzaldehyde (3 g, 15.2 mmol) described in Manufacturing Example 69-1-1, nitromethane (1.63 mL, 30.4 mmol), ammonium acetate (1.76 g, 22.8 mmol) and acetic acid (30 mL) was stirred for 6 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.2 g). This compound was used in the following reaction without being purified.

[Manufacturing Example 69-1-3] (4-(2-Nitro-ethyl)-phenyl)-phenyl-amine

[0863]

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[0864] To an acetic acid (3.2 mL) and dimethyl sulfoxide (54 mL) solution of (4-((E)-2-nitro-vinyl)-phenyl)-phenyl-amine

(3.2 g. 13.4 mmol) described in Manufacturing Example 69-12 was added sodium borohydride (811 mg, 21.4 mmol) at corn temperature while cooling appropriately. This mixture was stirred for 1 hour at room temperature. The mixture was partitioned into ethyl acetrae and water. The original layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the restidue was purified by silice gel column chromatography (heptane: ethyl acettae 4.1 - 2: 1) to obtain the title compound (201 g. 62%). H-NMR Spectrum (CDCL) 8 (ppm): 3.24-3.28(2H, m), 4.56-4.60 (2H, m), 5.81 (1 H, brs), 6.93-6.98 (1 H, m), 7.00-7.12 (6H, m), 7.00-7.12 (

[Manufacturing Example 69-1-4] (4-Phenylamino-phenyl)-acetohydroximoyl chloride

[0865]

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[0866] To a methanol (12 ml.) solution of (4-(2-nitro-ethyl)-phenyl)-phenyl-enine (1 g. 4.13 mmol) described in Manutchuring Example 88-1-3 was calcided lithium methodic (314 mg. 26 mnol). This instruct was attirred for 1 hour at room temperature. The mixture was concentrated under a reduced pressure, water in the residue was szeotropically distilled with toluene, and that residue was diluted with methylene chierdic (16 ml.), and tetrahydrofuran (7.6 ml.). This was cooled to -78°C, and tetrahum (fv) tetrachierdic gly99 ml., 9.09 mmol) was added dropwise into the suspension. The mixture was stirred for 1 hour at room temperature. This mixture was cooled to -78°C, and partitioned into ethyl ceetate and (ce water. The organic layer wes separated, washed with saturated equeous scolum choridor, dired over enhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.2 a). This compound was used in the following reaction without further purification.

[Example 70] 3-(3-(4-Butyl-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

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[0863] To a terrahydrouran (3 mL) solution of (4-butyl-phenyl)-eccelohydroximoyl chloride (150 mg, 0.656 mmol) described in Manufacturing Example 70-13 and 3-ethyryl-pridin-2-ylernine (50 mg, 0.424 mmol) described in Manufacturing Example 1-23 was added thethylamine (282 µL, 1.66 mmol) at room temperature, which was stirred for 8 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous osotium chloride, and dried over anthyrous magnesium sulfate, and the solvent was eveporated under a reduced pressure. The residue was purified by NH silica gel column chronidagraphy (heatmane: ethyl acetate = 4:1 - 2:1) to obtain the title compound (55 mg, 18%).

1-H-NMR Spectrum (CDCl₃) (ppm): 93-0.94 (31 m, 1.31-1.40 (2H, m), 1.55-1.63 (2H, m), 2.57-261 (2H, m), 4.03 (2H, s), 5.53 (2H, brs), 6.26 (1 H, s), 6.70 6.73 (1 H, m), 7.14-7.20 (4H, m), 7.71-7.73 (1H, m), 8.11-8.13 (1 H, m).

[0869] The starting material (4-butyl-phenyl-pacetorydroximous) chloride, was synthesized as follows:

[Manufacturing Example 70-1-1] 1-butyl-4-((E)-2-nitro-vinyl)-benzene

[0870]

[0871] A mixture of 4-n-buly/benzaldehyde (5 g, 30.8 mmol), nitromethane (3.31 mL, 61.6 mmol), ammonium acetate (3.55 g, 46.2 mmol) and acetic acid (50 mL) was stirred for 5 hours at 100°C. The mixture was cooled to room temperature, occentrated under a reduced pressure, and fulfuled with ethyl acetate. The organic layer was weshed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (5.7 g). This compound was used in the subsequent reaction without being purified.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 0.92-0.95(3H, m), 1.34-1.39(2H, m), 1.58-1.65(2H, m), 2.64-2.68(2H, m), 7.25-7.27 (2H, m), 7.45-7.48(2H, m), 7.56-7.59(1 H, m), 7.98-8.02(1 H, m).

[Manufacturing Example 70-1-2] 1-Butyl-4-(2-nitro-ethyl)-benzene

[0872]

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[0873] To an acotic acid (6.7 mL) and dimethyl sullovide (86 mL) solution of 1-buyll-4 ((E)2-nitro-vinyl-benzene (5.7 g. 27.8 mmol) described in Manufacturing Example 70-11 was added sodium borohydride (1.68 g. 44.5 mmol) at room temperature while cooling appropriately. This mixture was stirred for 3 hours at room temperature. The mixture was partitioned into ethyl acotato and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfat, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica get column chromatography (heptane: othyl acotate = 4 : 1 - 2 : 1) to obtain the title compound (1.48 g. 26%). 1H-NMR Spectrum (CDC4) 5 (ppm): 0.90-0.94(9H, m.), 1.31-1.37(2H, m.), 1.54-1.61(2H, m.), 2.56-2.60(2H, m.), 3.27-3.30 (2H, m.), 4.57-4.61 (2H, m.), 7.10-1.51(6H, m.).

[Manufacturing Example 70-1-3] (4-Butyl-phenyl)-acetohydroximoyl chloride

[0874]

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[0875] To a methanol (18 m.) solution of 1-but/h-4(-2-hitro-ethyl)-benzene (1.48 g, 7.14 mmol) described in Manufacturing Szampie 70-1-2 was added tilbium methodide (542 mg, 14.3 mmol). This influture was stirred for 1 hour at rome of the presenture. The mixture was concentrated under a reduced pressure, water in the residue was acvorpolically distillied with toluene, and that residue was disuled with methylene chloride (22 ml.) and tetrahydrofuran (11 ml.). This was cooled to 78°C, and titarium (IV) tetrachloride (1.7 ml., 15.7 mmol) was added dropvise into the suspension. This mixture was stirred for 1 hour at room temperature. This mixture was cooled to 78°C, and partitioned into ethyl acetate and ice water. The organic layer was separated, washed with saturated aqueous sodium chioride, dried over anythydrus mag-sensum sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.5 g). This compound was used in the subsequent reaction without further purification.

[Example 71] 3-(3-(6-(3-Fluoro-phenoxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0876]

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[0877] To a tetrahydroturan (4 mL) solution of 3-ethynyl-pytdin-2-ylamine [20 mg, 0.17 mm0] described in Manufacturing Example 1-2-3 and (6-34tuoro-phenoxy)-pytdin-2-yl-acetohydroximoy chloride (95 mg, 0.34 mmo) described in Manufacturing Example 71-1-4 was added triethylamine (47 µ, 0.34 mmo), which was stirred for 3 hours at 50°C under nitrogen atmosphere. Water was added to the reaction solution at room temperature, which was then extracted with ethyl scentar 1. The programment of the structured requests sodium chloride, dired over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the filtrate was purified by INH sillica gel column chromatography (ethyl acetate: methanol = 20°1) and further purified by reverse-phase high-performace liquid chromatography (stung an acetohicine-water mobile phase containing 0.1 % trifluoracetic acidy to obtain the title compound (33 mg, 33%) as a ditrifluoracetic acid salt.

[0878] The starting material, (6-(3-fluoro-phenoxy)-pyridin-3-yl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 71-1-1] 5-Bromo-2-(3-fluoro-phenoxy)-pyridine

[0879]

[0880] To an N,N-dimethylformamide (100 m.l.) solution of 3-fluorophenol (3.30 g, 29.4 mmol) was added sodium hydride (1.41 g. 29.4 mmol, 50% in oil), which was sitted for 10 mulnete at 0°C. 2-5 bibmonopytrian (4.64 g, 19.6 mmol) was then added to this mixture at 0°C, followed by 7 hours and 45 minutes of stirring at 110°C. Water was added to the exaction solution at morn temperature, which was het extracted with ethyl acetate. The organic layer was separated, washed with water and esturated aqueous solution thioride, dred over analyzious magnesium suitate, and fittered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptine: ethyl acetate 3: 1) to obtain the tild compound (5.3 g, quant.).

¹H-NMR Spectrum (DMSO-d_e) δ (ppm):7.00-7.02(1H, m), 7.08-7.13(3H, m), 7.43-7.49(1 H, m), 8.09(1 H, dd, J=2.8, 8.8 Hz), 8.31 (1 H, d, J=2.8 Hz).

[Manufacturing Example 71-1-2] 6-(3-Fluoro-phenoxy)-pyridine-3-carbaldehyde

[0881]

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[0882] To a ciertyl ether (100 mL) solution of 5-bromo-2(3-filhoro-phenoxy)-pyridine (6.81 g, 2.17 mmol) described in Manufacturing Example 71-1 was added no buyl lithium (13.8 mL, 15.7 M n-hexame solution, 2.17 mmol) under nitrogen atmosphere at -78°C, which was stirred for 40 minutes at -78°C. N.N-Dimethylformamide (2.02 mL, 26.0 mmol) was then added to the mixture at -78°C, and stirred for 25 minutes as the temperature was gradually raised to 0°C. Water was added to the reaction solution at 0°C, which was then extracted with ethyl acetate. The organic layer was separated, washed with 1 N aqueous sodium hydroxide solution and saturated aqueous sodium chloride, dried over anthyrous magnesium suitate, and fitteed. The filter was concentrated under a reduce pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 5:1) to obtain the title compound (2.47 g, 6794.)

¹H-NMR Spectrum (CDCl₃) δ (ppm):6.91-7.01(3H, m), 7.06(1H, d, J=8.8 Hz), 7.37-7.42(1 H, m), 8.20(1 H, dd, J=2.4, 8.4 Hz), 8.62(1 H, d, J=2.4 Hz), 9.98(1 H, s).

[Manufacturing Example 71-1-3] 2-(3-Fluoro-phenoxy)-5-(2-nitro-ethyl)-pyridine

[0883]

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[0884] To an acetic acid (20 mL) solution of 6+(3-fluoro-phenoxy)-pyridine-3-carbaldehyde (2.47g, 1.4mmol) operacined in Meanufacturing Example 7-11-2 was added informethane (3.0 mL, 5.70 mmol) and armonium seatest (1.76 g, 22.8 mmol), which was stirred for 6 hours at 100°C. Water was added to the reaction solution at room temperature, which was then extracted with eithy acetae. The organic losey was separated, washed with saturated augueus south choride, dired over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduce pressure. To a dimethyl sulfoxide (35 mL) and acetic acid (5 mL) solution of the residue was added sodium borohydride (881 mg, 1.71 mmol), which was stirred for 40 minutes at room temperature. Sodium hydrogenoarbonate and water were added to the reaction mixture at room temperature while cooling appropriately, which was then extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous codium chioride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica elections continued to the reaction of the residue was purified by NH silica election mixture and the residue was purified by NH silica elections and the residue was purified by NH silica elections and the residue was purified by NH silica elections and the residue was purified by NH silica elections and the residue was purified by NH silica elections. The residue was purified by NH silica elections and the residue was purified by NH silica elections. The first was concentrated under a reduced pressure, and the residue was purified by NH silica elections. The residue was purified by NH silica elections and the residue was purified by NH silica elections. The residue was purified by NH silica elections and the residue was purified by NH silica elections. The residue was purified by NH silica elections and the residue was purified by NH silica elections. The residue was purified by NH si

[Manufacturing Example 71-1-4] (6-(3-Fluoro-phenoxy)-pyridin-3-yl)-acetohydroximoyl chloride

[0885]

[0886] To a methanol (20 m.L) solution of 2 (3-fluoro-phenoxy) 5-(2-nitro-ethyl)-pyridine (1.96 g. 7.47 mmol) described in Manufacturing Example 71-1.3 was added lithium methods (667 mg. 143 mmol), which was sirred for 55 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. Trialmium (f) terachoride (1.81 ml., 16.4 mmol) was added under nitrogen atmosphere to a tetrahydrofuran (20 ml.) and methylene chloride (20 ml.) suspension of the residue, and stirred for 1 hour 15 minutes at 0°C. Water was added to the reaction mixture at 0°C, which was then extracted with eithyl acetale. The consideral verse resonant laver was separated, washed with saturated accues sodium

chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (2.1 g, quant). This compound was used in the subsequent reaction without further purification.

¹H-NMR Spectrum (CDCl₃) δ (ppm):3.77(2H, s), 6.87-6.95(4H, m), 7.31-7.38(1 H, m), 7.65(1 H, dd, J=2.6, 8.4 Hz), 8.12 (1 H, d, J=2.6 Hz).

[Example 72] 3-(3-(6-(4-Fluoro-phenoxymethyl)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0887]

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[0888] To a methanol (5.00 mL) solution of 2-(4-fluoro-phenoxymethyl)-5-(2-nitroethyl)-pyridine (50.0 mg, 0.181 mmol) described in Manufacturing Example 72-1-3 was added lithium methoxide (13,7 mg, 0,362 mmol) under nitrogen atmosphere at room temperature, which was stirred for 30 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure, and anhydrous dichloromethane (4.00 ml) and anhydrous tetrahydrofuran (2.00 ml) were added to the residue. Titanium (IV) chloride (63.7 µL, 0.579 mmol) was added dropwise into the reaction mixture on a dry ice-ethanol bath (-78°C), and stirred for 40 minutes at 0°C. Water and ethyl acetate were added to the reaction mixture on an ice bath (0°C), and the organic layer was extracted with ethyl acetate. This organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain a crude product (43.0 mg). To a tetrahydrofuran (5.00 mL) solution of this crude product (23.0 mg) and 3-ethynyl-pyridin-2-ylamine described in Manufacturing Example 1-2-3 (3.44 mg, 0.029 mmol) was added triethylamine (12.2 µL, 0.083 mmol) at room temperature, which was stirred for 2 hours at room temperature. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:2), the mixture was further purified by reverse-phase high-performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trifluoracetic acid) to obtain the title compound (3.62 mg, 25.4%) as a ditrifluoracetic acid salt. MS m/e(ESI) 377.18(MH+)

[0889] The starting material, 2-(4-fluoro-phenoxymethyl)-5-(2-nitro-ethyl)-pyridine, was synthesized as follows.

[Manufacturing Example 72-1-1] 5-Bromo-2-(4-fluoro-phenoxymethyl)-pyridine

[0890]

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[0891] To an N,N-dimethylfomamide (400 ml.) solution of 4-fluorophenol (3.00 g., 28.8 mmol) was added sodium hydride (1.00 g., 50 mmol, 69% in oil) on an ice buth ("O") under infragor atmosphere, which was stirred for 20 minutes at room temperature. To the reaction solution was then added a mixture of 5-brono-2-chloromethyl-pyridine hydrochloride (4.6 g., 22.3 mmol) described in Manufacturing Example 64-12- and triethylamine (30.6 ml., 2.0 mmol), which was stirred for 10 minutes at room temperature. Water and ethyl acetate were added to the reaction mixture, and the organic layer was extracted with ethyl acetate. This organic layer was exshed with water and saturated aqueous sodium chloride, died over anhydrous magnesium sulfate, and filtered. The solvent was evaporated from the filtrate under a reduced

pressure, and the residue was purified by silica gel column chromatography (ethyl acetate: heptane = 1:4) to obtain the title compound (4.0 q. 63.6%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.10 (2H, s), 6.88-6.91 (2H, m), 6.95-6.99 (2H, m), 7.40-7.42 (1 H, m), 7.81-7.84 (1 H, m), 8.64-8.65 (1 H, m).

[Manufacturing Example 72-1-2] 6-(4-Fluoro-phenoxymethyl)-pyridine-3-carbaldehyde

[0892]

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[0893] To a diethyl ether (100 mL) solution of 5-tromo-2-4-fluoro-phenoxymethyl)-pyridine (4.00 g, 14.2 mmol) described in Manufacturing Example 72-1-1 was added dropwise *n*-butyl tithium (2.55 M *n*-hexane solution, 6.13 mL, 15.6 mmol) on a dry ice-ethanol bath (-78°C) under nitrogen atmosphere, which was stirred for 40 minutes at -78°C. Nh. dimethylformamide (1.32 mL, 17.0 mmol) was then added dropwise and stirred for 5 minutes at -78°C. The reaction solution was cooled to room temperature and water was added, followed by extraction with ethyl acetate. The organic layer was washed with saturated equieous sodium chloride, and the solvent was exportated under a reduced pressure. The residue was purified by sitica gel column chromatography (ethyl acetate: heptane = 1: 4) to obtain the title compound (1.00 a; 30.5%).

¹H-NMR Spectrum (CDCl₃) δ ppm): 5.25 (2H, s), 6.91-7.02 (4H, m), 7.71-7.75 (1 H, m), 8.19-8.22 (1 H, m), 9.04-9.05 (1H, m), 10.12 (1 H, s).

[Manufacturing Example 72-1-3] 2-(4-Fluoro-phenoxymethyl)-5-(2-nitro-ethyl)-pyridine

[0894]

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[0895] To an acetic acid (5.00 m.), solution of 64.4-fluoro-phenoxymethyl-pyridrine-3-carbaidehyde (500 mg. 1.30 mmol) described in Manufacturing Example 72-1-2 were added nitromethane (923 mg. 15.1 mmol) and ammonium acetate (933 mg. 4.32 mmol) under nitrogen atmosphere, which was stirred for 2 hours at 10-5°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was extracted with eithyl acetate. The organic layer was washed with water and seturated aqueues sodium chloride, died over anhydrous magnesium sulfate, and filtered. The solvent was evaporated from the filtrate under a reduced pressure. Dimethyl sulfoxide (10.0 ml.) and acetic acid (600 nl.) were dided to the residue, and sodium borohydride (131 mg. 3.46 mmol) was then added at norm temperature while cooling appropriately. Following 20 minutes of stirring, water was added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride, died over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1: 1) to obtain the title compound (50 mg. 8.38%).

¹H-NMR Spectrum (DMSO-d₀) δ (ppm): 3.36 (2H, t, J=6.8 Hz), 4.96 (2H, t, J=6.8 Hz), 5.40 (2H, s), 7.01-7.05 (2H, m), 7.16-7.20 (2H, m), 7.84 (1 H, d, J=8.0 Hz), 8.17 (1 H, dd, J=2.0, 8.4 Hz), 8.75 (1 H, s).

[Example 73] 3-(3-(4-Phenylaminomethyl-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0896]

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[0887] To a tetrahydrofuran (3 mL) solution of (4-phenylaminomethy-phenyl-pacetohydroximoy) chloride (150 mg, 0.546 mmol) described in Manufacturing Example 7.3-6 and 3-ethyryl-pyridin-2-ylamine (4 mg, 0.348 mmol) described in Manufacturing Example 1.2-3 was added triethylamine (104 µL, 0.748 mmol), which was stirred for 7 hours at room temperature. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with water and saturated equeous sodium chloride and ridd over anylydrous megnesium suffate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane : ethyl acetate = 1: 1 - 1; 2) to obtain the title compound (11 mg, 6%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 4.05(2H, s), 4.32(2H, s), 5.39(2H, brs), 6.26(1H, s), 6.62-6.64(2H, m), 6.69-6.74 (2H, m), 7.15-7.23(5H, m), 7.34-7.36(2H, m), 7.69-7.72(1H, m), 8.13-8.15(1H, m).

[0898] The starting material, (4-phenylaminomethyl-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

25 [Manufacturing Example 73-1-11 4-[1.3] Dioxolan-2-vibenzaldehyde

[0899]

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39 [0900] To a tetrahydrofuran (100 mL) solution of 2-(4-bromo-phenyl)-1,3-doxolane (8 g, 3.4 pmmol) was added drop-wise n-butly lithium (19.6 mL, 2.67 M hexane solution, 52.4 mmol) at 78°C. After 1 hour of stirring at 78°C, Normyl-morpholine (4.42 g, 3.8.4 mmol) was added to the mixture, and stirred for 3 hours at the same temperature. This mixture was partitioned into diethyl ether and water. The organic layer was separated, washed with saturated aqueous sodum chroride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (6.3). This compound was used in the subsequent reaction without being purified.

1H-NMR Spectrum (CDCl₃) δ (ppm): 4.04-4.16(4H, m), 5.89(1 H, s), 7.65-7.67(2H, m), 7.90-7.92(2H, m), 10.0(1H, s).

[Manufacturing Example 73-1-2] (4-[1,3] Dioxolane-2-vl-benzyl)-phenyl-amine

45 [0901]

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[9902] To a tetrahydrofuran (200 ml.) solution of 4-[1,3] dioxolane-2-ybenzaldehyde (6.22 g, 35.5 mmo) described in Manufacturing Example 73-1-, aniline (20.8 ml., 35.5 mmo) and acetic acid (10.2 ml., 178 mmo) was added sodium triacetoxyborohydride (15 g, 71 mmo). This mixture was stirred for 1 hour at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (hepitane: ethyl acetate = 4: 1) to obtain the title compound (4.16 g, 46%). H-NMR Spectrum (COL) à (60m.) 4.20-4.16(6.1.m.), 4.35(21.4. b., 6.8 ft (11.4. b., 66.1-6.83(21.4. m.)6.6-6.73(11.4. m.)

7.14-7.18(2H, m), 7.38-7.40(2H, m), 7.45-7.47(2H, m).

[Manufacturing Example 73-1-3] 4-Phenylaminomethyl-benzaldehyde

[0903]

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[0904] To a mixture solution of methanol and tetrahydrofuran (1:1, 20 mL) of (4:1,3) dioxolane-2y-bear(yl)-pnenylamine (4.16 g, 16.3 mmol) described in Maurifacturing Example 73-12 was added 54 hydrochloric acid (20 mL). This mixture was strired for 1 hour at room temperature. This mixture was neutralized with saturated aqueous sodium hydrogencarionate solution, and extracted with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous rangensium suifate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.5 g). This compound was used in the subsequent reaction without being purified. H-NMM Spectrum (CDCL) is (growth, 31(H)t. Inst). 45(EH) a. (5.6 g-6.2(H) ml, 9.7.6-2(H) H, ml), 7.15-7.20(H, ml),

[Manufacturing Example 73-1-4] (4-((E)-2-nitro-vinyl)-benzyl)-phenyl-amine

7.53-7.55(2H, m), 7.84-7.87(2H, m), 10.0(1 H, s),

[0905]

[0966] A mixture of 4-phenylaminomethyl-benzaldenyle (6.5 g. 16.6 mmp) described in Manufacturing Example 73-13, nitromethane (4.46 mL, 83 mmol), ammonium acetate (2.66 g. 33.2 mmol) and acetic acid (30 mL) was stirred for 4 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with ethyl acetate. The organic layer was weshed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 10:1-4:1) to obtain the title compound (1.53 g. 36%). 1H-NMR Spectrum (CDCl₂) is (ppm): 4.16(H, brs), 4.42(2H, m), 6.60-6.82(2H, m), 6.72-6.76(1H, m), 7.15-7.19(2H, m), 7.54-7.47(2H, m), 7.51-7.53(2H, m), 7.58(H, d, d-13.8 Hz). 3.00(H, d, d-13.8 Hz).

40 [Manufacturing Example 73-1 -5] (4-(2-Nitro-ethyl)-benzyl)-phenyl-amine

[0907]

[0908] To an acetic acid (1.5 m.), and dimethyl sulfoxide (28 m.l.) solution of (4.(6)-2-nitro-vinyl)-benzyl-phenyl-amine (1.53 g. 6.02 mmol) described in Manufacturing Example 73-1-4 was added sodium borohydride (364 m.g. 9.63 mmol) at room temperature while cooling appropriately. This mixture was stried for 1.5 hours a troom temperature. This mixture was partitioned into eithyl acetate and water. The organic layer was separated, washed with water, dried over arrhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.5 g). This compound was used in the subsequent reaction without being purified.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.29-3.33(2H,m), 4.32(2H, s), 4.59-4.62(2H, m), 6.61-6.63(2H, m), 6.70-6.74(1H, m), 7.15-7.29(4H, m), 7.33-7.35(2H, m).

[Manufacturing Example 73-1-6] (4-Phenylaminomethyl-phenyl)-acetohydroximoyl chloride

[0909]

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[0910] To a methanol (24 mL) solution of (4-(2-nitro-ethyl)-benzyl)-phenyl-amine (1.5 g, 5.66 mmol) described in Manufacturing Example (24-16-was added lithium methaoide (430 mg, 1.13 mmol). This mixture was sirred for 1 hour at room temperature. This mixture was concentrated under a reduced pressure, water in the residue was azeotropically distilled with touene, and that residue was distuled with methylene chloride (25 mL) and tetrahydroturan (12.5 mL). This was cooled to -78°C, and itanium (iV) tetractionide (1.93 mL, 18.1 mmol) was added dropwise into the supersion. This mixture was stirred for 1 hour at room temperature. This mixture was cooled to -78°C and partitioned into ethyl acetate and ice water. The organic layer was separated, washed with saturated aqueous sodium chioride, died over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.5 g). This compound was used in the subsequent reaction without truther purification.

[Example 74] 3-(3-(6-(2-Fluoro-phenoxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamin

[0911]

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- 80 [0312] To a tetrahydroturan (1 m.l.) solution of 3-ethymyl-pyridin-2-ylamine (9.0 mg, 0.076 mmol) described in Manufacturing Example 1-2-3 and (6-(2-fluoro-phenoxy)-pyridine-3-yl)-acetohydroximoyl chloride (28 mg) described in Manufacturing Example 74-1-4 was added triethylamine (21 µL, 0.15 mmol), which was stirred for 5 hours at 55°C. The mixture was cooled to room temperature and water was added at that temperature, followed by extraction with ethyl acetate. The organic layer was washed with seturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (athyl acetate): heptane = 2 : 1) to obtain the title compound as a crude product. This was then purified by reverse-phase high-performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trilliovacetic acid). Triethylamine was added to make the solvent basic when concentrating the mobile phase, and the eluste was concentrated under a reduced pressure. The resulting residue was washed with water to obtain the title compound (1 o mg, 4%).
- ⁴⁵ ¹H-NMR Spectrum (CDCl₃) 8 (ppm): 4.01 (2H, s), 5.53 (2H, brs), 6.27 (1 H, s), 6.73 (1 H, dd, J=4.9, 7.7 Hz), 6.98 (1 H, d, J=8.4 Hz), 7.147-25 (4H, m), 7.83 (1 H, dd, J=2.4, 8.4 Hz), 7.72 (1 H, dd, J=1.8, 7.7 Hz), 8.09 (1 H, d, J=2.4 Hz), 8.14 (1 H, dd, J=1.9, 4.9 Hz)
 - [0913] The starting material, (6-(2-fluoro-phenoxy)-pyridin-3-yl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 74-1-1] 5-Bromo-2-(2-fluoro-phenoxy)-pyridine

[0914]

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10 [0915] To a mixture of 2-fluorophenol (2.1 g, 19 mmol), 2.5-dibromopyridine (3.0 g, 13 mmol) and N.N-dimethytionamide (30 mL) was added sodum) hydride (20 mg, 15 mmol, 50% in oil) at 6°C, which was estimed for 10 minutes at room temperature. The reaction mixture was then stirred for 5 hours at 110°C. The reaction mixture was cooled to room temperature and water was added, followed by extrection with eithyl actains. The organic layer was washed twice with water and then washed with saturated queueus sodium chloride, was concentrated under a reduced pressure. The reaction was purified by NH-ellioa gelcolumn chromatography (heptane: ethyl acetate = 15:1) to obtain the title compound (940 mg, 25%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 6.91-6.93 (1H, m), 7.16-7.24 (4H, m), 7.79 (1 H, ddd, J=0.6, 2.6, 8.6 Hz), 8.17 (1 H, dd, J=0.6, 2.6 Hz).

20 [Manufacturing Example 74-1-2] 6-(2-Fluoro-phenoxy)-pyridine-3-carbaldehyde

[0916]

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[0917] To a mixture of 5-bromo-2-(2-fluore-phenoxy)-pyridine (500 mg, 1.9 mmol) described in Manufacturing Example 74-1-1 and textrahydrofursor in 70.1 was added n-buyl lithium (1.7 mt, 1.5 M n-buxane solution, 2.6 mmol) under nitrogen atmosphere at -78°C. Ni, N-dimethylformamide (0.29 mL, 3.7 mmol) was added to the reaction mixture at the same temperature, and the temperature was then gradually raised to 0°C. Water was added to the reaction broad to was then contracted with eithy actient. The residue was purified by silica gel column chromatography (heptane : ethyl scettare | 2.1 in to obtain the title compound (210 mb, 53%).

 1 H-NMR Spectrum (CDCl₃) 3 (ppm): 7.12-7.15 (1 H, m), 7.20-7.31 (4H, m), 8.22 (1 H, dd, J=2.4, 8.6 Hz), 8.60 (1 H, dd, J=0.6, 2.4 Hz), 9.99 (1 H, d, J=0.6 Hz).

[Manufacturing Example 74-1-3] 2-(2-Fluoro-phenoxy)-5-(2-nitro-ethyl)-pyridine

[0918]

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[0919] To a mixture of 6-(2-fluoro-phenoxy)-pyridine-3-carbaldehyde (210 mg, 0.97 mmol) described in Manufacturing

Example 74.1-2 and acetic acid (3 m.l), were added nitromethane (0.39 m.l., 7.3 mmol) and ammonium acetate (220 m.g. 2.9 mmol), which was stirred for 3 hours at 100°C. The reaction mixture was cooled to room temperature and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated aqueous sodium chioride and dried over anhydrous magnesium sulfate, and was concentrated under a reduced pressure. A mixture of methyl subscite (6 m.l.) and acetace acid (0.2 m.l.) was added to the resulting residue, and sodium brorbydride (68 m.g. 1.5 mmol) was added to the reaction mixture was added to the reaction mixture was stirred for 10 minuties. Water was added to the reaction at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane : ethyl acetate = 2 : 1) to obtain the title compound if (50 m. 6, 1 %).

1H-NMR Spectrum (CDCl₃) δ (ppm): 3.28 (2H, t, J=7.1 Hz), 4.59 (2H, t, J=7.1 Hz), 6.97 (1 H, d, J=8.4 Hz), 7.15-7.24 (4H, m), 7.57 (1H, dd, J=2.6, 8.4 Hz), 8.00 (1H, d, J=2.6 Hz).

[Manufacturing Example 74-1-4] (6-(2-Fluoro-phenoxy)-pyridin-3-yl)-acetohydroximoyl chloride

[0920]

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[0921] To a mixture of 2-(2-fluoro-phenoxy)-5-(2-nitro-ethyl)-pyridine (150 mg, 0.59 mmol) described in Manufacturing Example 74-1-3 and methanol (1.5 mi), was added liftium methoxide (45 mg, 1.2 mmol) at room temperature, which was sirred for 5 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure. Titanium (IV) chloride (140 µL, 1.3 mmol) was added at -76°C to a mixture of the resulting residue, methylene chloride (2 ml.) and tetrahydrofurur (1 ml.), and sittered of 90 minutes at 0°C. The reaction mixture was colded to 78°C, water (1 ml.) was added, and the temperature was gradually raised to room temperature. Water was added to the reaction southing and troom temperature, which was then extracted with eithyl acetate. The organic layer was washed with water until the pH was 5, and then washed with saturated aqueous sodium chloride. The organic layer was died over anhydrous magnesium suifate, and was concentrated under a reduced pressure to obtain the title compound (160 mg) as a crude product. This compound was used in the subsequent reaction without further purification.

11-NMR Spectrum (CDCs) 6 (ppm): 3.74 (2H, s), 6.97 (1 H, d, J=8.4 Hz), 7.15-7.25 (4H, m), 7.83 (1 H, dd, J=2.4, 8.4 Hz), 8.04 (1 H, b, J=2.0 Hz).

(Example 75] 3-(3-(6-(4-Fluoro-phenoxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0922]

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[0923] To a mixture of (6·(4-fluore-phenoxy)-pyridin-3-yl)-acetohydroximoyl chloride (25 mg) described in Manufacturing Example 75-14 and tetrahydroturun (1 mL) were added 3-ethynyl-pyridin-2-ylarnine (6.0 mg, 0.051 mmo) described in Manufacturing Example 1-23 and triethylamine (21 µL, 0.15 mmo), which was stred for 6 hours at 55°C. The reaction mixture was cooled to room temperature and water was added thereto at that temperature, followed by extraction with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH siting agle column chromatography (lefty) acetate:

heptane = 2:1) to obtain the title compound (5.9 mg, 32%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 4.02 (2H, s), 5.41 (2H, br s), 6.27 (1 H, s), 6.73 (1 H, dd, J=4.8, 7.7 Hz), 6.90 (1 H, d, J=4.4 Hz), 7.06-7.12 (4H, m), 7.62 (1 H, dd, J=2.6, 8.4 Hz), 7.71 (1 H, dd, J=1.7, 7.6 Hz), 8.13 (1 H, d, J=2.6 Hz), 8.16 (1 H, dd, J=1.7, 4.9 Hz)

[0924] The starting material, (6-(4-fluoro-phenoxy)-pyridin-3-yl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 75-1-1] 5-Bromo-2-(4-fluoro-phenoxy)-pyridine

10 [0925]

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29 [0926] To a mixture of 4-fluoropheno (2.1 g, 19 mmol), 2.5-dibromopyridine (3.0 g, 13 mmol) and N.N-dimethyformamide (30 mL) was added sodium hydride (730 mg, 15 mmol, 50% in oil) at 0°C, which was stirred for 10 minutes at room temperature. The reaction mixture was then stirred for 5 hours at 110°C. The reaction mixture was wooled to room temperature and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with water twice, and then washed with saturated aqueous sodium-chloride, and was connectrated under a reduced pressure, set of the residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 15: 1) to obtain the title compound (2 e. a. 75%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 6.83-6.85 (1 H, m), 7.09 (4H, d, J=6.4 Hz), 7.76-7.79 (1 H, m), 8.20 (1 H, dd, J=0.6, 2.6 Hz)

[Manufacturing Example 75-1-2] 6-(4-Fluoro-phenoxy)-pyridine-3-carbaldehyde

[0927]

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[0928] To a mixture of 5-bromo-2-(4-fluoro-phenoxy)-pyridine [940 mg, 3.5 mmol) described in Marufacturing Example 75-11 and fathery dorfuna (10m.) was added n-buly likhium (1.7 mt. 1.5 M n-hexanes solution, 2.6 mmol) under introgen atmosphere at -78°C, which was stirred for 30 minutes at that temperature. N. N-dimethylformamide (0.54 mt., 7.0 mmol) was added to the reaction in mixture at the same temperature, and the temperature was gradually risaded to "OX bulk was added to the reaction solution, which was then extracted with ethyl accetate. The originic layer was washed with saturated aqueous sodium chioride, and was concentrated under a reduced pressure. The residue was purified by silica gle column chromatography (heptican: ethyl accetate = 2 : 1) to obtain the title compound (280 mg, 36%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 7.04-7.06 (1 H, m), 7.13-7.15 (4H, m), 8.20 (1 H, ddd, J=0.9, 2.4, 8.6 Hz), 8.61 (1 H, dd, J=0.6, 2.4 Hz), 9.99 (1 H, d, J=0.6 Hz).

[Manufacturing Example 75-1-3] 2-(4-Fluoro-phenoxy)-5-(2-nitro-ethyl)-pyridine

[0929]

[9830] To a mixture of 6:4-fluore-phenoxy)-pyridine-3-carbatelehyde (150 mg, 0.69 mmol) described in Menufacturing Example 76-1:2 and acetic acid (2mL) were added nitremethane (228 mL, 5.2 mmol) and ammonium ceatate (180 mg, 2.1 mmol), which was stirred for 5 hours at 100°C. The reaction mixture was cooled to room temperature and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated aqueous sodium chioride and diried over anhydrous magnesium sulfate, and was concentrated under a reduced pressure. A mixture of dimethyl sulfoxide (3 mL) and seetic acid (0.2 mL) was added to the resulfing residue, and sodium borohydride (22 mg, 1.1 mmol) was added at momenture was the memperature. Which cooling appropriately. The reaction mixture was stirred for 10 minutes at that temperature. Water was added at mom temperature to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic larger was washed with saturated aqueous sodium chioride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane : ethyl acetate z-11) to obtain the title compound (130 mg, 70%).

 1 H-NMR Spectrum (CDCl₃) δ (ppm): 3.28 (2H, t, J=7.1 Hz), 4.60 (2H, t, J=7.1 Hz), 6.89 (1 H, dd, J=0.4, 8.4 Hz), 7.09 (4H, d, J=6.4 Hz), 7.55 (1 H, dd, J=2.6, 8.4 Hz), 8.03 (1 H, d, J=2.2 Hz).

[Manufacturing Example 75-1-4] (6-(4-Fluoro-phenoxy)-pyridin-3-yl)-acetohydroximoyl chloride

[0931]

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[0932] To a mixture of 24.4-fluoro-phenoxy)-5-{2-nitro-ethyl-pyridine (120 mg, 0.46 mmol) described in Manufacturing Example 75-1.3 and methanol (2 mL) was added lithium nethoxide (35 mg, 0.91 mmol) at room temperature, which was stirred for 5 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. A mixture of methylene chindrie (2 mL) and tetrahydrofuran (1 mL) was added to the residue, and titrahum (IV) chloride (1 mL) L, 1.0 mmol) was added to the reaction mixture was cooled to 0°C, vater (1 mL) was added, and the temperature was gradually raised to room temperature. Water was added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with water until the pri was 5, and then washed with saturated aqueous sodium chloride. The organic layer was difed over antrydrous magnesium suifate, and was concentrated under a reduced pressure to obtain the title compound (130 mg) as a crude product. This compound was used in the subsequent reaction without further purification.

[Example 76] 3-(3-(4-(Pyridin-3-yloxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0933]

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[0934] To a methanol (10.0 mL) solution of 3-(4-(2-nitro-ethyl)-phenoxy)-pyridine (819 mg, 3.35 mmol) described in Manufacturing Example 76-1-3 was added lithium methoxide (254 mg, 6.70 mmol) under nitrogen atmosphere at room temperature, which was stirred for 30 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure, and anhydrous dichloromethane (15.0 ml) and anhydrous tetrahydrofuran (7.00 mL) were added to the residue. Titanium (IV) chloride (1.18 ml., 10.7 mmol) was added dropwise to the reaction mixture on a dry ice-ethanol bath (-78°C), and stirred for 30 minutes at room temperature. Sodium bicarbonate solution and ethyl acetate were added to the reaction mixture on an ice bath (0°C), which was then filtered through a Celite pad. The organic layer of the filtrate was extracted with ethyl acetate, and that organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain a crude product (400 mg), To a tetrahydrofuran (5.00 mL) solution of this crude product (250 mg) and 3-ethynyl-pyridin-2-ylamine described in Manufacturing Example 1-2-3 (40.0 mg, 0.339 mmol) was added triethylamine (142 a.L. 1.02 mmol) at room temperature, which was stirred for 3 hours at 60°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 1 : 1), the mixture was further purified by reverse-phase high-performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trifluoracetic acid) to obtain the title compound (11.7 mg, 10.0%) as a ditrifluoracetic acid salt.

MS m/e(ESI) 345.13(MH+)

⁹ 1H-NMR Spectrum (CD₃OD) ô (ppm): 4.17 (2H, s), 6.89 (1 H, s), 7.08-7.10 (1H, m), 7.19-7.22 (2H, m), 7.48-8.50 (2H, m), 7.94-7.39 (1H, m), 8.04-8.06 (1H, m), 8.08-8.11 (1 H, m), 8.37-8.39 (1 H, m), 8.55 (1 H, d, J=5.6Hz), 8.60 (1 H, d, J=2.8Hz).

[0935] The starting material, 3-(4-(2-nitro-ethyl)phenoxy)-pyridine, was synthesized as follows.

25 [Manufacturing Example 76-1-1] 4-(Pvridine-3-vloxy)-benzaldehyde

[0936]

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[0937] To, an N, N-dimethylformamide (30.0 mL) solution of 3-hydroxypyridine (3.00 g, 31.5 mmol) and 4-fluoroberzaleichyde (5.0 g, 4.10 mmol) was added potassium carbonate (8.17 g, 6.30 mmol) under nitrogen embosphere, which was stirred for 17 hours at 70°C. The reaction mixture was then cooled to room temperature and water was added thereto, followed by extraction with eithyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced-pressure. The residue was purified by silica gel column chromatography (ethyl acetate: heptane = 1:1 -> 3:1) to obtain the title compound (1.70 g, 27.1%). 1+MMR Spectrum (CDCL)§ (pomy 7.09-7.11 (2H, m), 7.85-7.93 (H, m), 7.41-7.44 (H, m), 7.88-7.91 (2H, m), 8.48-8.51

(2H, m), 9.96 (1 H, s).

45 [Manufacturing Example 76-1-2] 3-(4-((E)-2-Nitro-vinyl)-phenoxy)-pyridine

[0938]

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[0939] To an acetic acid (17.0 mL) solution of 4-(pyridine-3-yloxy)-benzaldehyde (1.70 g, 8.53 mmol) described in Manufacturing Example 76-1-1 were added nitromethane (2.60 g, 42.7 mmol) and ammonium acetate (1.32 g, 17.1

mmol) under nitrogen atmosphere, which was stirred for 3 hours at 110°C. Water and ethyl acetate were added to the reaction solution, and the organic layer was then extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (2,00 at sa crude product.

⁵ ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 7.12-7.14 (2H, m), 7.48-7.51 (1H, m), 7.57-7.61 (1 H, m), 7.91-7.94 (2H, m), 8.16-8.19 (2H, m), 8.46-8.47 (2H, m).

[Manufacturing Example 76-1-3] 3-(4-(2-Nitro-ethyl)-phenoxy)-pyridine

0 [0940]

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[0941] To a dimethyl sulfoxide (15.0 m.l.) solution of 3-(4-(16)-2-nitro-invi)y-hencovy)-pyridine (2.00 g. a.28 mmol) described in Manufacturing Example 76-1-2 and acetic acid (2.00 m.l.) was added sodium borohydride (500 mg. 13.2 mmol) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 30 minutes at room temperature. Water was then added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chioride, dried over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was cyrified by NHs islic gel column chromatography (ethyl acetate: heptane = 1:3 → 1:2) to obtain the title compound (819 mo. 40 %).

 $^{1}\text{H-NMR Spectrum (DMSO-d_g)} \, \delta \, (\text{ppm}) \cdot 3.26 \, (2\text{H, t, J=6.8Hz}), \, 4.88 \, (2\text{H, t, J=6.8Hz}), \, 7.17 \, (2\text{H, d, J=8.4Hz}), \, 7.40 \, (2\text{H, d, J=8.4Hz}), \, 7.68 \cdot 7.76 \, (2\text{H, m}), \, 8.23 \, (1\text{H, s}), \, 8.35 \, (1\text{ H, d, J=5.2Hz}).$

[Example 77] 3-(3-(4-(Thiophen-3-ylinethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0942]

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[0943] To a tetrahydroturan (3 m.l.) solution of (4-(thiophen-3-ymethoxyl-phenyl)-excelohydroximoy chloride (150 m.g. 052 mmol) described in Manufacturing Example 7-14 and 3-ethynyl-yndin-2-ylamine (4 mg. 0,338 mmol) described in Manufacturing Example 1-2-3 was added thethylamine (185 µ.l., 1.33 mmol), which was stirred for 3 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with eithyl acetae. The organic layer was washed with water and saturated equeues sodium chloride and dried over enhydrous magnetism suffate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silice gel column chromatography (heplane: ethyl acetate -4:1-2:1-1:1) to obtain the title compound (46 mg. 24%).

1H-NMR Spectrum (CDCL) & (ppm): 4.00(2H, a), 5.06(2H, s), 5.41(2H, brs), 6.24(1H, s), 6.99-6.72(1 H, m), 6.93-6.95 (2H, m), 71.4-715(1H, m), 7.19-7.22(2H, m), 73.7-53(2H, m), 79.9-7.71 (1 H, m), 8.19-8.14(1H, m) (19044)
[Ost4] The starting material, (4-(thiophen-3-yimethoxy)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

55 [Manufacturing Example 77-1-1] 4-(Thiophen-3-ylmethoxy)-benzaldehyde

[0945]

[0946] To a tetrahyurduran (250 ml.) solution of diethylazodicarboxylate (16.1 ml., 40.9 mmol) were added 4-hydroxybenzaldehyde (5 g., 40.9 mmol), 3-thiophene methanol (3.86 ml., 40.9 mmol) and PS-triphenylphosphine (29 g., 1.41 mmol/g, 40.9 mmol). This mixture was stirred for 7 hours at room temperature. This mixture was concentrated under a reduced pressure, and the residue was purified by silica gel column chromalography (heptane: ethyl acetate = 2:1) to obtain the title comozound (3.61 o., 40%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 5.17(2H, s), 7.07-7.09(2H, m), 7.15-7.17(1 H, m), 7.35-7.39(2H,m), 7.84-7.86(2H, m), 9.90(1 H, s).

5 [Manufacturing Example 77-1-2] 3-(4-((E)-2-Nitro-vinyl)-phenoxymethyl)-thiophene

[0947]

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[0949] A mixture of 4-(thiophen-3-yimethoxy)-benzaldehyde (3.61 g, 16.5 mmol) described in Manufacturing Example 77-1-1, nitromethane (4.4 mt., 8.25 mmol), amonolum acetate (2.5 g, 33 mmol) and acetace acid (36 mt.) was stirred for 5 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with ethyl acetaet. The organic leyer-was washed with waster and saturated aqueous oxidium chioride, efficie dover anylydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (4,1 o).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.14(2H, s), 7.01-7.03(2H, m), 7.14-7.16(1H, m), 7.34-7.35(1 H, m), 7.37-7.39(1 H, m), 7.50-7.54(3H, m), 7.96-8.00(1 H, m).

[Manufacturing Example 77-1-3] 3-(4-(2-Nitro-ethyl)-phenoxymethyl)-thiophene

[0949]

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[0950] To an acetic acid (4, 1 m.l.) and dimetrly sufficial (70 m.l.) solution of 3-(4-((6)-2-nitro-winyl)-phenoxymetrly)+Thi-ophene (4.1 g, 15.7 mmol) described in Manufacturing Example 77-1-2 was added acidium borohydride (950 mg, 25.1 mmol) at room temperature while cooling appropriatuly. This mixture was stirred for 1.5 hours at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dired over analydrous magnesium surfact, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 4:1-2:1) to obtain the title compound (1,93 q, 47%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.24-3.28(2H, m), 4.55-4.59(2H, m), 5.05(2H, s), 6.91-6.93(2H, m), 7.11-7.15(3H, m), 7.31-7.32(1H, m), 7.34-7.38(1H, m).

[Manufacturing Example 77-1-4] (4-(Thiophen-3-ylmethoxy)-phenyl)-acetohydroximoyl chloride

[0951]

[0952] To a methanol (12 mL) solution of 3/4-(2-nitro-ethyl-phenoxymethyl-thiophenot (1 g. 3.8 mmol) described in Manufacturing Exempler 77-13 was added filthum methode (28 mg., 7.6 mmol). This instrue was stirred for 1.5 hours at room temperature. The mixture was concentrated under a reduced pressure, water in the residue was executopically distilled with foluene, and that residue was distuted with methylene chloride (16 mL) and tetrahydroturan (8 mL). This was cooled to 78°C, and tilianium (IV) tetrachioride (1.3 mL, 122 mmol) was added dropwise into the suspension. This mixture was stirred for 1 hour at room temperature. This mixture was cooled to 78°C and partitioned into ethyl acetate and to ewter. The organic layer was separated, washed with saturated equeues sodium chindrick, died over arhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.1 o.1) This compound was used in the subsequent reaction without further purification.

[Manufacturing Example 78] 3-(3-(4-Cyclopentyloxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0953]

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[0954] To a tetrahydroturan (3m.l.) solution of (4-cyclopentylox-yhenyl)-acetohydroximoyi chioride (150 mg.) cammol described in Manufacturing Example 78-1 and 3-d-thynyl-yhenide 2-described in Manufacturing Example 12-3 (45 mg.) 0.378 mmol) was added triethylamine (206 µL, 1.48 mmol), which was stirred for 3 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was vashed with water and saturated aqueous sodium chloride and dried over anhydrous magnesium sultate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl scatetale 4:1:1-2:1) to obtain the title compound (44 mg., 22%).

1H-MMR Spectrum (CDCL) & (ppm): 157-175(2H, m), 1.75-1.92(8H, m), 3.98(2H, s), 4.71-4.75(1H, m), 5.39(2H, brs), 6.24(1H, s), 6.69-6.72(1H, m), 6.82-6.85(2H, m), 7.16-7.18(2H, m), 7.69-7.71 (1H, m), 8.12-8.14(1H, m) (1995) The starting material, (4-cyclopentyloxy-phenyl)-acethyldroximoyl chloride, was synthesized as follows.

[Manufacturing Example 78-1-1] 4-Cyclopentyloxy-benzaldehyde

[0956]

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[9957] To a tetrallydrofuran (250 mL) solution of diethylazodicarboxylate (16.1 mL, 40.9 mmol) were added 4 hydroxybenzaldehyde (6, g. 4.09 mmol), oclopentanol (3,1 mL, 4.09 mmol) and triphenyhybrosphine (10.7, g. 4.09 mmol). This mixture was stirred for 30 minutes at room temperature. The mixture was concentrated under a reduced pressure, and the residue was purified by silicea der cloumen chromatography the plane; eithyl acetate = 2: 11 to blash in the title compound. (4.36 g, 56%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 1.61-1,70(2H, m), 1.77-2.00(6H, m), 4.84-4.87(1 H, m), 6.95-6.98(2H, m), 7.80-7.83 (2H, m), 9.87(1H, s).

5 [Manufacturing Example 78-1-2] 1-Cyclopentyloxy-4-((E)-2-nitro-vinyl-benzene

[0958]

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[0959] A mixture of 4-cyclopentyloxy-benzaldehyde (4.36 g, 22.9 mmol) described in Manufacturing Exemple 78-1-1, nitromethane (6.16 ml., 115 mmol), ammonium aceitate (3.53 g, 33 mmol) and aceits aceit (45 ml.) was stirred for 14 bnurs at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with eithyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dided over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (4.8 d).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.61-1.66(2H, m), 1.78-1.97(6H, m), 4.80-4.84(1 H, m), 6.90-6.93(2H, m), 7.46-7.53 (3H, m), 7.96-7.99(1 H, m).

25 [Manufacturing Example 78-1-3] 1-Cyclopentyloxy-4-(2-nitro-ethyl)-benzene

[0960]

[0861] To an acelic acid (4.8 m.l.) and dimethyl sulfoxide (82 m.l.) solution of 1-cyclopentyloxy4-4(E)-2-nîro-vinyl-benzaen (4.8 g. 20.4 mmol) described in Manufacturing Example 76-1-2 was added sodium borohyaride (1.2 g. 3, 82.6 mmol) at room temperature while cooling appropriately. The mixture was stirred for 1.5 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anytyrcous magnesium sutifact, and filtered. The filter was concentrated under a reduced pressure, and the residue was purified by silice gel column chromatography (heptane: ethyl acetate = 4:1-2:1) to obtain the title compound (3.24 g, 68%).

¹H-NMR Spectrum (CDCl₃) 8 (ppm): 1.59-1.65(2H, m), 1.76-1.92(6H, m), 3.23-3.27(2H, m), 4.55-4.58(2H, m), 4.70-4.74 (1 H, m), 6.80-6.84(2H, m), 7.07-7.11 (2H, m).

[Manufacturing Example 78-1-4] (4-Cyclopentyloxy-phenyl)-acetohydroximoyl chloride

[0962]

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CI-N

[0963] To a methanol (12 mL) solution of 1-cyclopentyloxy-4-(2-nitro-ethyl)-benzene (1 g, 4.26 mmol) described in

Manufacturing Example 78-1-3 was added lithium methoxide (565 m.g. 9.37 mmol). This micture was stirred for 1.5 hours at room temperature. The mixture was concentrated under a reduced pressure, water in the residue was azeotropically distilled with boutene, and that residue was diluted with methylene chloride (16 ml.) and tetrahydroturan (8 ml.). This was cooled to 78°C, and titanium (IV) tetrachloride (1.03 ml., 9.37 mmol) was added dropwise into the suspension. This mixture was stirred for 1 hour at room temperature. This mixture was cooled to 76°C and partitioned into ethyl acetate and ice water. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium surfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.1). This compound was used in the subsequent reaction without further purification.

[Example 79] 3-(3-(4-Cyclohexyloxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0964]

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[0965] To a tetrahydroturan (3 m.l.) solution of (4-cyclohexyloxy-phenyl)-acetohydroximoyl chioride (150 mg, 0.56 mmo) described in Manufacturing Example 1-2-3 was added triefhylamine (195 μ L, 1.4 mmo)), which was stirred for 4 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl section. The order was washed with water and saturated equeue us coldinary chioride and dried over analydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane : ethyl sectate = 4:1-2:1) to obtain the title compound (37 mg, 19%).

1H-NMR Spectrum (CDCl₂) 5 (ppm): 1.29-1.41(3H, m), 1.47-1.56(3H, m), 1.79-1.80(2H, m), 1.96-1.99(2H, m), 3.90(2H, s), 4.18-4.24(1 H, m), 5.38(2H, brs), 6.25(1 H, s), 6.69-6.72(1 H, m), 6.85-6.88(2H, m), 7.12-7.18(2H, m), 7.99-7.71 (1 H, m), 8.13-8.14(1 H, m).

[0966] The starting material, (4-cyclohexyloxy-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 79-1-1] 4-Cyclohexyloxy-benzaldehyde

[0967]

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[0988] To a tetralydrofuran (250 ml.) solution of diethylazodicarboxylate (16.1 ml., 40.9 mmol) were added 4-hydroxy-benzaldehyde (5 g., 40.9 mmol), cyclohexanol (4.31 ml., 40.9 mmol) and triphenylphosphine (10.7 g., 40.9 mmol). This mixture was stirred for 30 hours at room temperature. The mixture was concentrated under a reduced pressure, and 5the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 2:1) to obtain the title compound (2.8 4 g., 34%).

 1 H-NMR Spectrum (CDCl₃) 3 (ppm): 1.31-1.46(4H, m), 1.53-1.63(2H, m), 1.80-1.86(2H, m), 1.98-2.02(2H, m), 4.35-4.41 (1 H, m), 6.97-7.00(2H, m), 7.80-7.84(2H, m), 9.87(1 H, s).

55 [Manufacturing Example 79-1-2] 1-Cyclohexyloxy-4-((E)-2-nitro-vinyl)-benzene

[0969]

[0970] A mixture of 4-cyclohexyloxy-benzalatehyde (2.84 g, 13.9 mmor) described in Manufacturing Exemple 79-1-1, intromethane (3.4 mt, 8.9 5 mmol), ammonium acetate (2.14 g, 2.8 mmol) and acetal ceid (30 mt), was sirred for 14 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with ethyl acetate. The organic layer was washed with saturated estipeous sodium chloride, dried over anhydrous magnesium suitae, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.3 g).

14-MMR Spectrum (CDCJ) (Sppm): 1:34-1.45(8H; m), 1.51-1.51 (8H; m), 1.80-1.82(2H; m), 1.99-2.00(2H; m), 4.31-4.38 (1H; m), 5.91-6.85(2H; m), 7.85-7.50(2H; m), 7.85-7.57 (1H; m), 7.89-7.99(1H; m).

[Manufacturing Example 79-1-3] 1-Cyclohexyloxy-4-(2-nitro-ethyl)-benzene

[0971]

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[0972] To an acetic acid (3.3 mL) and dimethyl sulfoxide (56 mL) solution of 1-cyclohexylory-4-(Fc)2-ntiro-vinyl)-benzene (3.3 g, 13.1 mmol) described in Manufacturing Example 79-1-2 was added sodium borohydride (793 mg, 21 mmol) at room temperature while cooling appropriately. This mixture was settined for 1 hour at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 4 : 1) to obtain the title compound (1.45 g, 44%). 1H-NMR Spectrum (CDClg) & (ppm): 1.26-1.48(9H, m), 1.46-1.58(9H, m), 1.79-1.81(2H, m), 1.95-1.98(2H, m), 3.23-3.27 (2H, m), 4.17-4.241 H, m), 4.56-8.68(2H, m), 6.83-8.77(2H, m), 7.09-1.70(2H, m)

[Manufacturing Example 79-1-4] (4-Cyclohexyloxy-phenyl)-acetohydroximoyl chloride

[0973]

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[0974] To a methanol (17 m.) solution of 1-cyclohexyloxy-4(2-nitro-ethyl)-benzene (1.45 g. 5.82 mmo) described in Manufacturing Example 29-13 was added tithium methavide (420 m.), 16 mmol.) This mixture was striend for 2 hours at room temperature. The mixture was concentrated under a reduced pressure, water in the residue was zerocropically distilled with tolurers, and that residue was diluted with methylene chloride (24 ml.) and tetrahydrofuran (12 ml.). This was cooled to 7-8°C, and titanium (IV) tetrachioride (1.41 ml., 128 mmol) was added dropwise into the suspension. This mixture was solved to 7-8°C and partitioned into ethyl categories with the control of the suspension of the control of the cont

[Example 80] 3-(3-(4-(2-Furan-2-yl-ethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0975]

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N NH₂

[0976] To an anhydrous tetrahydrofuran (5 mL) solution of 3-ethynyl-pyridin-2-ylamine (33.1 mg, 0.281 mmoi) described in Manufacturing Example 1-2-3 was added (4-(2-furan-2-yl-ethyl) phenyl-acetohydroxinoy) chloride (224 mg, 0.85 mmoi) described in Manufacturing Example 0-1-7 under hitrogen atmosphere at room temperature. The irrehylamine (0.24 ml, 1.7 mmoi) was then added dropwise, followed by 1.5 hours of stirring at 60°C. The reaction mixture was pertitioned into water and ethyl acetate at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride and dried over anhydrous magnesium suifale, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 1 : 9 then 3 : 7) to obtain the title compound (3.6 km, 4.0 8%).

1H-NMR Spectrum (CDCl₂) 6 (ppm): 2.88-2.98 (4H, m), 4.03(2H, s), 5.41 (2H, brs), 5.97 (1 H, d, J=3.2 Hz), 6.25(1 H, s), 6.27 (1 H, dd, J=2.0 Hz), 7.70 (1 H, dd, J=0.0, 8.0 Hz), 7.15(2H, d, J=8.4 Hz), 7.20 (2H, d, J=8.4 Hz), 7.31 (1 H, d, J=0.1 Hz), 7.70 (1 H, dd, J=0.0, 8.0 Hz), 8.13 (1 H, dd, J=0.4 Hz), 7.70 (1 H, dd, J=0.0, 8.0 Hz), 8.13 (1 H, dd, J=0.4 Hz), 7.81 (1 Hz)

5 [0977] The starting material, ((4-(2-furan-2-yl-ethyl) phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 80-1-1] 4-((E)-2-furan-2-yi-vinyl)-benzoic acid ethyl ester

[0978]

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[0978] 60% Sodium hydride (0.48 g. 12 mmol) was suspended in anhydrous tetrahydroturan (10 mL) under hitrogen atmosphere, and diethyl 4-chtosycathomyl benzylohosphonate (3.6) g. 12 mmol) prepared from elhyl 4-bromomethyl-benzoate and triethylphosphite according to the methods as similar to those of Manufacturing Example 93-1-1 was added at room temperature, and stirred of 30 minutes at room temperature. Furthrait (1 g. 10.4 mmol) was then added at room temperature, and stirred for 2 hours at room temperature. The reaction mixture was partitioned into water and ethy acetate on an ice bath (0°C). The organic layer was washed with water and saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was exportated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 1:20) to obtain the title compound (1.07, 42%).

¹H-NMR Spectrum (CDCl₂) δ (ppm): 1.40 (3H, t, J=5.2Hz), 4.38(2H, q, J=5.2Hz), 6.40-6.48 (2H, m), 6.99(1H, d, J=16Hz), 7.05(1H, d, J=16Hz), 7.43(1H, m), 7.50(2H, dd, J=2.0, 6.4Hz), 8.01 (2H, dd, J=2.0, 6.4Hz).

[Manufacturing Example 80-1-2] 4-(2-Furan-2-vi-ethyl)-benzoic acid ethyl ester

[0980]

[0881]. To an anhydrous tetrahydrofuran (25 mL) solution of 4-(E)-2-furan-2-yl-viny)-benzoic acid ethyl easter (1.07 g, 4.4 mmol) described in Manufacturing Example 80-1-1 was added 10% palladium-carbon (50% hydrate, 500 mg), which was stirred for 2 hours under a hydrogen atmosphere at room temperature. The reaction product was tiflered, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (butlymethyl ether: heptane 6 : 5) 910 to obtain the till compound (706 mg, 65.4%).

H-NMR Spectrum (CDCl₃) δ (ppm): 1.39 (3H, t, J=7.2Hz), 2.90-3.08(4H, m), 4.36 (2H, q, J=7.2Hz), 5.94(1 H, m), 6.26 (1 H, m), 7.21 (2H, d, J=8.0Hz), 7.32 (1 H, m), 7.95(2H, d, J=8.0Hz).

[Manufacturing Example 80-1-3] (4-(2-Furan-2-yl-ethyl)-phenyl)-methanol

109821

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[0883] To an aninydrous tetrahydrofuran (10 mL) solution of stilly 4-(2-furan-2-yi-stilly)-benzolo acid ethly ester (706 mg, 2.89 mmol) described in Manufacturing Exemple 80-1-2 was acided discolutyl aluminum hydride (0.97 M toluene solution, 7.45 mL, 7.23 mmol) on a dry ice-ethanol bath (-78°C) under nitrogen atmosphere. After 30 minutes of stirring, 15% aqueous potassium sodium teatrates solution (40 mL) was acided to the reaction solution, and stirred for 90 minutes at room temperature. Ethly acted (100 mL) was added, and the organic layer and water layer were separated. The organic layer was washed with water and saturated aqueous sodium chloride and dried over anhydrous magnesium sufface, and the solvent was evaporated under a reduced pressure to obtain the title compound (660 mg, 99%). HH-NMR Spectrum (CDCla) 6 (ppm): 1.58 (1 H, I), 3-6.0 Hz), 2.90-3.00(4H, m), 4.66 (2H, d, J=6.0 Hz), 5.96(1 H, m), 6.27 (1.1H, m), 7.17(2H, d, J=6.0 Hz), 7.28(2H, d, J=6.0 Hz), 7.32(H, m).

[Manufacturing Example 80-1-4] 4-(2-Furan-2-yl-ethyl)-benzaldehyde

[0984]

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[0985] To an ethyl acetate (50 mL) solution of (4-(2-furan-2-yl-ethyl)-phenyl)-methanol (580 mg, 2.87 mmol) described in Manufacturing Example 80-1-3 was added activated manganese dioxide (8 g, 92 mmol), which was stirred for 12 hours at room temperature. The reaction solution was suction filtered through a Celling and, and washed with ethyl acetate (50 mL). The filtrate was concentrated under a reduced pressure to obtain the title compound (480 mg, 83.5%). HH-NMR Spectrum (CDCl₃) δ (ppm): 2.94-3.08(4H, m), 5.96(1H,m), 6.27(1H,m), 7.32(3H, d, J=8.0Hz), 7.80(2H, d, J=8.0Hz), 9.96(1 H, s).

[Manufacturing Example 80-1-5] 4-(2-Furan-2-yl-ethyl)-((E)-2-nitro-vinyl)-benzene

[0986]

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o-N-

[0987] To an acetic acid (5 ml.) solution of 4(2-furan-2y-lethyl-benzaldehylde (480 mg, 2.4 mmol) described in Manufacturing Example 80-1-4 were added nitromethane (732 mg, 1.2 mmol) and ammonium acetate (370 mg, 4.8 mmol) under nitrogen atmosphere at room temperature, which was stirred for 2 hours at 120°C. The reaction mixture was partitioned into water and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium choirde and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure to obtain the title compound (554 mg, 95%) as a crude product.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.90-3.08(4H, m), 5.95 (1 H, m), 6.27 (1 H, m), 7.23(2H, d, J=8.0Hz), 7.32(1H,m), 7.46(2H, d, J=8.0Hz), 7.57(1H, d, J=13.6Hz), 7.99(1H, d, J=13.6Hz).

[Manufacturing Example 80-1-6] 4-(2-Furan-2-yl-ethyl)-(2-nitro-ethyl)-benzene

[0988]

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o-M-

[0889] To a mixed tertahydrofuran-dimethyl sulfoxide (111, 10 ml.) solution of 4(2-furan-2-yl-ethyl-(E)-2-thro-vi-myl)-benzene (554 mg, 2.28 mmol) described in Manufacturing Example 80-1-5 and acetic acid (0.5 ml.) was added sodium borothydride (129 mg, 3.42 mmol) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 10 minutes at room temperature. Water was added dropwise into this reaction solution at room temperature while cooling appropriately. The reaction mixture was partitioned into water and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (buyimptily) ether. beptane = 5: 99) to obtain the title compound (300 mg, 53%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.88-2.96 (4H, m), 3.29 (2H, t, J=7.2Hz), 4.59 (2H, t, J=7.2Hz), 5.95(1 H, m), 6.27 (1H, m), 7.10-7.16(4H, m), 7.32(1H, m)

[Manufacturing Example 80-1-7] (4-(2-Furan-2-yl-ethyl) phenyl)-acetohydroximoyl chloride

[0990]

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[0991] To a methanol (5 mL) solution of 4-(2-furan-2-yf-ethyl)-(2-nitro-ethyl)-benzene (300 mg, 1.22 mmol) described in Manufacturing Exemple 80-1-6 was added lithium methoxide (92.7 mg, 2.44 mmol) under nitrogen atmosphere at croom temperature, which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under

a reduced pressure. Anhydrous methylene chloride (7 mL) and anhydrous tetrahydrofuran (3 mL) were added to the residue. A filtanium (IV) chloride (2.7 mL, 1 M dichloromethane solution 2.7 mmn) was added dropwise into the reaction mixture on a tily cee thand bath (78°C), which was stured for 45 minutes at 0°C. Water and ethyl acetax were added to the reaction mixture on an ice bath (0°C), and the organic layer was separated. This organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressyre to obtain the tite compound (324 mg. 100%).

 1 H-NMR Spectrum (CDCl₃) 3 (ppm): 2.88-2.96 (4H, m), 3.77 (2H, s), 5.96(1 H, m), 6.27(1 H, m), 7.15 (2H, d, J= 8.4Hz), 7.19 (2H, d, J= 8.4Hz), 7.32(1 H, m), 7.36 (1 H, s).

Example 81] 3-(3-(4-(3-Fluoro-phenoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[0992]

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[0993] To a tetrahydrolivan (5.00 mL) solution of (4:0-fluoro-phenoxy-phenyl)-acetohydroxmoyl chiords (280 mg, 1.04 mmo) losseibed in Manufacturing Example 81-12 and 3-ethynyl-pyridin-2-ylamine described in Manufacturing Example 12-23 (50.0 mg, 0.423 mmol) was added tristhylamine (177 µL, 1.27 mmol) at room temperature, which was stirred for 30 minutes at 60°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chioride and dried over antrydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NI+ silica el column chromatoparaby (eithy lacetate: hepotage = 1 5) to lotatin the tible comound (3.87 m. p.2.5.3%).

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 4.05 (2H, s), 6.27 (2H, brs), 6.70 (1 H, dd, J=3.2, 8.0Hz), 6.79-6.93 (2H, m), 6.84 (1 H, s), 6.95 (1 H, m), 7.04-7.06 (2H, m), 7.37-743 (9H, m), 7.88 (1 H, dd, J=1.6, 8.0Hz), 8.09-8.10 (1 H, m), 7.94-7.06 (2H, m), 7.37-74 (9H, m), 7.88 (1 H, dd, J=1.6, 8.0Hz), 8.09-8.10 (1 H, m), 9.09-8.10 (1 H, m), 9.09-9.10 (1 H, m), 9.0

[Manufacturing Example 81-1-1] 1-(3-Fluoro-phenoxy)-4-(2-nitro-ethyl)-benzene

[0995]

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[0999] To an N,N-dimetry(formamide (30,0 mL) solution of 3-fluorophenol (5.4.9, 4.8.4 mmol) and 4-fluorobenzaideptide (3.0.0.9, 2.4 mmol) was added potassium carbonate (1.0.1.9, 2.5 mmol) under introgen atmosphere, which was stirred for 16 hours at 60°C. The reaction mixture was cooled to room temperature and water was added, followed by extraction with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and the selvent was eveporated under a reduced pressure. The residue was purified by silice get column chromatography (ethyl acetate) is heptane = 1:15 -> 1:10) to obtain a mixture with the starting material (6.00 g). To an acetic acid (500 mL) solution of this mixture (6.0) givere added informedhare (6.7.8 g, 111 mmol) and ammonium acetate (3.4.9, 4.4 mmol) at room temperature, which was stirred for 4 hours at 110°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnessium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain a crude product (6.6 g). To a dimethy sulfoxide (4.00 mL) solution of this crude product (6.6 g) and acetic acid (5.00 mL) was added sodium borothydride (1.28 g, 3.3 mmol) at room temperature while cooling appropriately, with was sittered for 5 minutes at norm temperature. appropriately. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:5) to drain the title comocond (2:10: a.3.79%).

1H-NMR Spectrum (DMSO-d_e) δ (ppm): 3.24 (2H, t, J=6.8Hz), 4.86 (2H, t, J=6.8Hz), 6.78-6.85 (2H, m), 6.94-6.98 (1 H, m), 7.03 (2H, d, J=8.0Hz), 7.33 (2H, d, J=8.0Hz), 7.40-7.42 (1 H, m).

[Manufacturing Example 81-1-2] (4-(3-Fluoro-phenoxy)-phenyl)-acetohydroximoyl chloride

[0997]

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[0988] To a methanol (10.0 mL) solution of 1-(3-fluoro-phenoxy)-4-(2-nltro-ethyl)-benzene (500 mg, 1.91 mmol) described in Manufacturing Example 8-1-1 was added lithium methoxide (145 mg, 3.82 mmol) under nitrogen at mosphere at own temperature, which was stirred for 30 minutes at room temperature. The solvent was evaporated from the filtrate under a reduced pressure, and anhydrous dichicromethane (2.0.0 mL) and anhydrous tetrahydrofuran (10.0 mL) were added to the residue. Titanium (IV) chloride (325 a, L.4.78 mmol) was added dropwise into the reaction mixture on a rise plant of the reaction mixture on an ice ball with the reaction mixture on an ice ball with the reaction mixture on an ice ball (O°C), and the organic layer was extracted with eithy a celestate. The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was connectrated under a reduced pressure to obtain the title compound (440 mg) 9.17% ja sa crude product. 11-1.4 mL 9.17 mL 9

[Example 82]3-(3-(4-(2-(Tetrahydrofuran-2-yl)-ethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[09991

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[1000] To an anhydrous tetrahydrofuran (5 mL) solution of 3-ethynyl-pryidin-2ylamine described in Manufacturing Example 1-2-3 (43.7 mg, 0.37 mmol) was added (4/2-letrahydrofuran-2yl-ethyl) phenyl)-bectohydroximoyi chlorida (300 mg, 11.2 mmol) described in Manufacturing Example 82-1-6 under nitrogen atmosphere at room temperature. Triethyemine (0.31 mL, 2.24 mmol) was then added dropwise and stirred for 2 hours at 60°C. The reaction mixture was partitioned into water and ethyl acetate at room temperature. The organic layer was washed with water and saturated aqueous sodium-chloride, and dried over anhydrous magnesium sulfate, and the solvent was eveporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: heptane =1:9 then 3: 7) to obtain the title comoround (68 m. 53%).

1H-NMR Spectrum (CDCl₉) & (ppm): 1.40-1.55(1H, m), 1.70-2.00(5H, m), 2.60-2.80(2H, m), 3.70-3.90(3H, m), 4.02(2H, s), 5.41 (2H, brs), 6.25 (1 H, s), 6.70(1 H, dd, J=4.8, 8.0Hz), 7.16-7.24(4H, m), 7.70 (1 H, dd, J=2.0, 8.0Hz), 8.13 (1 H, dd, J=2.0, 4.8Hz).

55 [1001] The starting material, (4-(2-tetrahydrofuran-2-yl-ethyl) phenyl)-acetohydroximoyl chloride, was synthesized as follows. [Manufacturing Example 82-1-1] 4-(2-(Tetrahydrofuran-2-yl)-ethyl)-benzoic acid ethyl ester

[1002]

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[1003] To an anhydrous tetrahydrofuran (25 ml.) solution of 4-((E)-2-furan-2-yl-vinyl)-benzoic acid ethyl ester (2.2 g, 9.9 mmol) described in Manufacturing Example 80-1-1 was added 10% palladium-carbon (60% hydrate, 1 g), which was stirred for flours under hydrogen atmosphere at room temperature. The reaction liquid was filtered, and the filtrate was concentrated under a reduced pressure to obtain the titte compound (2.2 g, 100%) as a crude product.

[Manufacturing Example 82-1-2] (4-(2-(Tetrahydrofuran-2-vi)-ethvl)-phenvl)-methanol

20 [1004]

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[1005] To an anhydrous tetrahydrofuran (20 mL) solution of ethyl 4-(2-(tetrahydrofuran-2-yf)-ethyl)-benzolo acid ethyl ester (2.2 g, 3.9 mm)) described in Manufacturing Example 82-1-1 was acided dislocutyl aluminum hydride (0.9 T M toluene solution, 24.2 mL, 25.5 mmol) on a dry ice-ethanol bath (7-8°C) under nifrogen atmosphere. After stirling for 30 minutes, 15% aqueous potassium sodium tartrate solution (100 mL) was added to the reaction liquid, and stirred for 30 minutes at room temperature. After addition of ethyl acetate (200 mL), the organic layer and water layer were separated. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium suffate, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate i-leptane = 1 - 9 then 2 : 9) to obtain the title compound (600 mg, 31%).

14-14MR Spectrum (CDCl₃) δ (ppm): 1.40-1.55 (1 H, m), 1.83 (1 H, t, J=6.0Hz), 1.70-2.00 (5H, m), 2.60-2.80 (2H, m), 3.70-3.90 (3H, m), 4.66 (2H, a.5-6.0Hz), 7.12 (2H, d.5-9.6Hz), 7.12 (2H, d.5-9.6Hz).

[Manufacturing Example 82-1-3] 4-(2-(Tetrahydrofuran-2-yl)-ethyl)-benzaldehyde

[1006]

[1007] To an ethyl acetate (50 mL) solution of (4/2-(letrahydrofuran-2-yf)-ethyf)-phenyl)-methanol (600 mg, 2.91 mmol) described in Manufacturing Example 82-1-2 was added active manganese dioxide (10 g, 115 mmol), which was stirred for 12 hours at room temperature. The reaction liquid was suction filtered through Ceitle pad, and washed with ethyl acetate (50 mL). The filtrate was concentrated under a reduced pressure to obtain the titls compound (565 mg, 95%) in H-NMR Spectrum (CDCl₃) & (ppm); 1.40-1.56 (1 H, m), 1.70-2.00 (5H, m), 2.60-2.80 (2H, m), 3.70-3.90 (3H, m), 7.37 (2H, d, J=8.4Hz), 7.80 (2H, d, J=8.0Hz), 9.97 (1H, s).

[Manufacturing Example 82-1-4] 4-(2-(Tetrahydrofuran-2-yl)-ethyl)-((E)-2-nitro-vinyl)-benzene

[1008]

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0-11-

[1009] To an acetic acid (10 mL), solution of 4-(2-(tetrahydrofuran-2-yf)-ethyl)-benzaidehyde (365 mg, 2.77 mmo) described in Manufacturing Example 82-1-3 were added nitromethane (1.69 g, 27.7 mmo) and ammonium acetate (427 mg, 5.54 mmo) under nitrogen atmosphere at room temperature, which was stirred for 4-hours at 120°C. The reaction mixture was partitioned into water and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chioride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure to obtain the title compound (646 mg, 94%) as a crude product.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.40-1.55 (1 H, m), 1.70-2.00 (5H, m), 2.60-2.80 (2H, m), 3.70-3.90 (3H, m), 7.29 (2H, d, J=8.0Hz), 7.47 (2H, d, J=8.0Hz), 7.57 (1H, d, J=13.6Hz), 7.99 (1 H, d, J=13.6Hz).

[Manufacturing Example 82-1-5] 4-(2-(Tetrahydrofuran-2-yl)-ethyl)-(2-nitro-ethyl)-benzene

[1010]

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o-Mining of

[1011] To a mixed tertahydroturan-dimethyl sulfoxide (1:1, 10 m.l.) solution of 4-(2-(tertahydrofuvran-2-y))-ethyl-((2)-2-intro-viny)-bearzen (648 fing. 2.61 mmol) described in Manufacturing Example 82-14 and aceta (ad (0.6 m.l.) was added sodium borohydride (148 mg, 3.92 mmol) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 10 minutes at room temperature. Water was added dropvise into the reaction mixture at room temperature while cooling appropriately. The reaction mixture was partitioned into water and erity acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by HH-silica gel column chromatography (ethyl acetate: heptane = 2: 8) to obtain the title compound (421 mg, 65%).

45 [Manufacturing Example 82-1-6] (4-(2-(Tetrahydrofuran-2-yl)-ethyl) phenyl)-acetohydroximoyl chloride

3.70-3.90 (3H, m), 4.59 (2H, t, J=7.2Hz), 7.11 (2H, d, J=8.4Hz), 7.17 (2H, d, J=8.4Hz)

[1012]

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[1013] To a methanol (5 mL) solution of 4(-2(-tetahydrofuran-2-y)-ethyh-(2-nitroethyl)-benzene (421 mg 1,69 mmol) described in Manufacturing Example 82-1-5 was added lithium methoxide (128 mg, 9.38 mmol) under nitrogen atmosphere at room temperature, and which was stirred for 30 minutes at room temperature. The reaction mixture was

concentrated under a reduced pressure. Anhydrous methylene chloride (10 mL), and anhydrous letrahydrofuran (5 mL) were added to the residue. A titanium (IV) chloride (1 M dichloromethane solution, 3.7 mL, 3.72 mmol) was added dropwise into the reaction mixture on a dry ice-ethanol bath (78°C), which was stirred for 45 minutes at 0°C. Water and ethyl acetate were added to the reaction mixture on an ice bath (0°C), and the organic layer was separated. The organic layer was usefave with water and saturated aqueous sodium chloride and dried over anthydrous magnesium suifate, and the solvent was evaporated under a reduced pressure to obtain the title compound (445 mg, 98%) as a crude product. 1H-NMR Spectrum (CDCs) (opm): 1.40-1.55 (1 H, m), 1.70-2.00 (5H, m), 2.60-2.80 (2H, m), 3.70-3.90 (3H, m), 3.77 (2H, s), 7.18 (H, bs), 7.51 (H, hb); b).

© [Example 83] 3-(3-(4-(2-Fluoro-phenoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1014]

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[1015] To a tetrahydroturan (10.0 mL) solution of (4/2-fluor-phenoxy-phenyl-acetohydroximoy(chloride (200 mg, 10.4 mm) described in Manufacturing Example 31-3 and 3-ethynyl-pyridin-2-ylamine (50.0 mg, 0.423 mmo) described in Manufacturing Example 1-23 was added triethylamine (177 µL, 1.27 mmo) at room temperature, which was stirred for 30 minutes at 60°C. Water was added to the reaction solution at room temperature, which was then extracted with erly acetate. The organic layer was washed with saturated aqueous osdium chindred and dried over anthyrdous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chinomatomarby (ethil acetate: heptate = 1: 510 to obtain the file compound (57.0 mg, 37.3%).

1H-NMR Spectrum (DMSO-d_b) 3 (ppm): 4.02 (2H, s), 6.27 (2H, brs), 6.81-6.72 (1 H, m), 6.82 (1 H, s), 6.94 (2H, d, J=8.4Hz), 7.13-7.18 (1 H, m), 7.20-7.25 (2H, m), 7.33 (2H, d, J=8.4Hz), 7.36-7.41 (1 H, m), 7.87-7.89 (1 H, m), 8.08-8.10

[1016] The starting material, (4-(2-fluoro-phenoxy)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

85 [Manufacturing Example 83-1-1] 4-(2-Fluoro-phenoxy)-benzaldehyde

[1017]

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[1018] To an N.N-dimethylomamide (93.0 mL) solution of 2-fluorophenol (6.4.9, 4.8.4 mmol) and 4-fluoroberatide (10.1, 9.2.5 mmol) under intripoge almosphere, which was stirred for 16 hours at 80°C. Water was added to the reaction solution at room temperature, which was then extracted with ethylacetate at 80°C grain leyers as wadered with earth earth earth and an additional molecular and the solution and the solution and the solution and the solution was exported under a reduced pressure. The residue was purified by silica get column chromatography (ethyl acetate: heptane = 1: 15 - 1: 1: 10) to estain the title commound (5.2.0 a.9.4%).

¹H-NMR Spectrum (CDCl₂) δ (ppm): 7.04 (2H, d, J=8.8Hz), 7.17-7.24 (4H, m), 7.85 (2H, d, J=8.8Hz), 9.91 (1H, s)

Manufacturing Example 83-1-2] 1-(2-Fluoro-phenoxy)-4-(2-nitro-ethyl)-benzene

[1019]

1020] To an acetic acid (30.0 mL) solution of 4(2-fluor-ophenoxy)-benzaldehyde (3.00 g, 13.9 mmol) described in Manufacturing Example 83-11 were added intermethena (42.4 g, 69.5 mmol) and ammonium acetate (2.14 g, 27.8 mmol) under nitrogen atmosphere, which was stirred for 8 hours at 110°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium-chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain a crude product (3.69 g). To a dimethyl sulfoxide (50.0 mL) solution of this crude product (3.69 g) and acetic acid (3.00 mL) was added sodium borolydride (789 mg, 20.9 mmol) at room temperature while cooling appropriately, which was stirred for 20 minutes at norn temperature. Water was then added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chloromatography (ethyl) exetates. The patent of the title compound (1.89 g, 49.6%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.20 (2H, d, J=7.2 Hz), 4.83 (2H, d, J=7.2 Hz), 6.91-6.93 (2H, m), 7.13-7.17 (1 H. m), 7.20-7.29 (4H, m), 7.36-7.41 (1 H. m).

[Manufacturing Example 83-1-3] (4-(2-Fluoro-phenoxy)-phenyl)-acetohydroximoyl chloride

[1021]

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HO_N O F

Id22] To a methanol (20.0 mL) solution of 1-(2-fluoro-phenoxy)-4-(2-ntro-ethyl)-benzene (1.80 g, 6.89 mmol) described in Manufacturing Example 83-1-2 was added lithium methoxide (524 mg, 13.8 mmol) under nitrogen atmosphere at noon temperature, which was stirred for 30 minutes at noon temperature. The reaction mixture was concentrated under a reduced pressure, and anhydrous dichloromethane (15.0 mL) and anhydrous tetrahydrofuran (5.00 mL) were added to the readule. Tatamium (IV) cholded (1.74 mL, 15.8 mmol) was added dropwise into the reaction mixture on a log vio-erthanol bath (-78°C), which was stirred for 30 minutes at noon temperature. Water, ethyl acetate and tetrahydrofuran were added to the reaction mixture on an loe bath (0°C), and the organic layer was extracted with ethyl acetate. This organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and fiftered. The fiftrate was concentrated under a reduced pressure to obtain the title compound (2.00 g, 51.9%) as a crude product.

45 1H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.79 (2H, s), 6.93-6.95 (2H, m), 7.16-7.27 (5H, m), 7.28-7.42 (1 H, m), 11.73 (1 H, s).

[Example 84] 3-(3-(3-Pyridin-2-yl-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

50 [1023]

N N

10 [1024] To a mixture of (3-(pyridin-2-yl)-phenyl)-acolohydroximoyl chloride (100 mg) described in Manufacturing Example 84-13 and tatrahydroluran (2 ml) were added 3 entrynly pyridin-2 yarinne (10 mg), 0.20 mmol) described in Manufacturing Example 1-2-3 and inethylamine (71 µL, 0.51 mmol) at room temperature, which was stirred for 2.5 house at 55°C. The reaction mixture was cooled to room temperature, and water was added at that temperature, followed by extraction with ethyl scortat. The organic layer was washed with saturated aqueues sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 2: 1) to obtain the title compound as a crude product. This was then purified by reverse-phase high-performance liquid chromotography (using an acetoritifle water mobile phase containing 0.1 % trifluoracetic acid) to obtain the title compound (7.2 mg, 15%) as a ditrifluoracetic acid salt.

MS m/et/ESI 302 20/MHY

[1025] The starting material, (3-(pyridin-2-yl)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 84-1-1] 3-Pyridin-2-yl-benzaldehyde

[1026]

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 $\prod_{i=1}^{n} \prod_{j=1}^{n} \prod_{i=1}^{n} \prod_{j=1}^{n} \prod_{j=1}^{n} \prod_{j=1}^{n} \prod_{i=1}^{n} \prod_{j=1}^{n} \prod_{i=1}^{n} \prod_{j=1}^{n} \prod_{j$

[1027] To a mixture of 3-bromobenzaldehyde (930 mg, 5.0 mmol) and toluene (10 mL) were added tri-n-butyl (2-pyridy) tin (2.1 g, 5.6 mmol) and bistriphenythosphine) palladium (II) chloride (350 mg, 0.50 mmol), and the reaction mixture was relieved for 5 hours. The reaction mixture was cooled to room temperature, and saturated equeous posassium fluoride solution (1 mL) was added at that temperature and stirred for 30 minutes at room temperature. Water and ethyl acetate were added to the reaction mixture, which was then filtered through a Celite pad. The organic layer of the filtrate was separated and washed with saturated aqueous sodium chloride. The solvent was evaporated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 2: 1) to obtain the title compound (350 mg, 58%).

¹H-NMR Spectrum (CDCl₂) δ (ppm): 7.28-7.32 (1 H, m), 7.65 (1H, t, J=7.7Hz), 7.80-7.82 (2H, m), 7.93-7.95 (1 H, m), 8.29-8.31 (1H, m), 8.50-8.51 (1 H, m), 8.72-8.74 (1 H, m), 10.12 (1H, s).

45 [Manufacturing Example 84-1-2] 2-(3-(2-Nitro-ethyl)-phenyl)-pyridine

[1028]

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[1029] To a mixture of 3-pyridin-2-yt-benzadehyde (290 mg, 1.6 mmol) described in Manufacturing Example 64-1-1 and ascele acid for Im) were added inthormethane (66 fm. 1,2 mmol) and amonium aceted (370 mg, 48 mmol), which was stirred for 2 hours at 100°C. The reaction mixture was cooled to room temperature and water was added, followed by actraction with stufy acetate. The organic layer was washed with sattured as quoesus sodium chloride and dried over antrydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. A mixture of dimethy is ultoxide (6 mt.) and acetc acid (0.4 mt.) was added to the resulting residue, and sodium borohydride (97 mg, 2.6 mmol) was added at room temperature. Water was added to the resulting residue, and sodium borohydride (97 mg, 2.6 mmol) was added at room temperature. Water was added to be reaction mixture at room temperature, which was then extracted with ethyl scottate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The resulting residue was purified by NH sitica gel column chromatography (heptane: ethyl acetate = 2:1) to obtain the title compound (260 mg, 71%).

1H-NMR Spectrum (CDCl₃)δ (ppm): 3.41 (2H, t, J=7.5Hz), 4.67 (2H, t, J=7.5Hz), 7.24-7.27 (2H, m), 7.44 (1 H, t, J=7.7Hz), 7.70-7.79 (2H, m), 7.85 (1H, d, J=7.9Hz), 7.90 (1 H, s), 8.68-8.70 (1H, m).

5 [Manufacturing Example 84-1-3] (3-(Pyridin-2-yl)-phenyl)-acetohydroximoyl chloride

[1030]

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[1031] To a mixture of 2-(8-(2-nitro-ethyl)-phenyl)-pyridine (260 mg, 1.1 mmol) described in Manufacturing Exemple 44-12 and methanol (4 ml.) was added lithium methodic (66 mg, 2.3 mmol) at room temperature, which was stirred for 5 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. A mixture of methylene chloride (6 ml.) and tetrahydrofuran (6 ml.) was added to the resulting reduce, and titalium (IV) chloride (400 μL, 3.6 mmol) was added to the reaction mixture at -76°C and stirred for 60 minutes at 0°C. The reaction mixture was cooled to 0°C and saturated aqueous sodium hydrogen carbonets solution was added at that temperature, followed by water and erthyl acetate. The reaction mixture was selfered through a Cellite paq, and the original layer of the filtrate was separated. The original layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium sultale, and was then filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (160 mg) as a crude product. This compound was used in the subsequent reaction without further purification.

[6 [Example 85] 3-(3-Biphenyl-3-ylmethyl-isoxazol-5-yl)-pyridin-2-ylamine

[1032]

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[1033] To a mixture of biphenyl 3-yl-acetohydroximoyl chloride (120 mg) described in Manufacturing Example 85-13 and tetrahydrofuran (8 mf.) were added 3-athynyl-pyridin-2-ylamine (28 mg. 0.24 mmol) described in Manufacturing Example 19-23 and triethylamine (20 µL, 1.4 mmol) at room temperature, which was stirred for 2.5 hours at 55°C. The reaction mixture was cooled to room temperature and water was added at that temperature, followed by extraction with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH sition ael column formantography (eithyl acetate: The chance 2 : 1)

to obtain the title compound (27 mg, 34%).

1H-NMR Spectrum (CDCl₂) δ (ppm): 4.13 (2H, s), 5.41 (2H, br s), 6.28 (1 H, s), 6.70 (1 H, dd, J=4.9, 7.7Hz), 7.27 (1 H, d, J=7.7Hz), 7.33-7.37 (1 H, m), 7.40-7.46 (3H, m), 7.50 (2H, d, J=6.8Hz), 7.56-7.59 (2H, m), 7.70 (1 H, dd, J=1.8, 7.7Hz), 8.13 (H, dd, J=1.4, 4.9Hz).

[1034] The starting material, biphenyl-3-yl-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 85-1-1] 3-Phenyl-benzaldehyde

[1035]

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0 [1056] To a mixture of 3-bromobiphenyl (0.50 mL, 3.0 mmol) and tetrahydrofuran (8 mL) was added n-buty lithium (2.6 mL, 1.5 m hexaens obtains, 3.9 mmol) under nitrogen attrosphere at 7-8°C, which was stiffed for 20 minutes at that temperature. N,N-dimethylformamide (0.35 mL, 4.5 mmol) was added to the reaction mixture at the same temperature, and the temperature was greated using the control of the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by slica gel column chromatography (heptane: ethyl acetate = 6: 1) to dorshi her lithic commond (430 mg, 79%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 7.38-7.42 (1 H, m), 7.46-7.50 (2H, m), 7.60-7.64 (3H, m), 7.86 (2H, dd, J=1.7, 7.9Hz), 8.11 (1 H, t, J=1.8Hz), 10.09 (1 H, s).

[Manufacturing Example 85-1-2] 3-(2-Nitro-ethyl)-biphenyl

[1037]

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[1038] To a mixture of 3-phenyl-berazidehyde (490 mg, 2.4 mmol) described in Manufacturing Example 85-1-1 and seale said (7 ml.) were added intromethane (9.85 ml., 18 mmol) and ammonium scattle (540 mg, 7.1 mmol), which was stirred for 2.5 hours at 100°C. The reaction mixture was cooled to room temperature, and water was added at the same temperature, followed by extraction with ethyl scotate. The organic layer was washed with saturated aqueous sodium chloride and dried over amydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. A mixture of dimethyl sulfoxide (9.3 ml.) and sectic acid (0.62 ml.) was added to the resulting residue, and sodium borohydride (140 mg. 3.8 mmol) was added to the reaction mixture at room temperature white cooling appropriately.

The reaction mixture was stirred for 10 minutes at the same temperature. Water was added to the reaction solution at room temperature, which was then extracted with ethyl scateta. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The resulting residue was purified by NH silica get column chromatography (heptane: ethyl acetets = 5:1) to obtain the title compound (380 mg, 71 %).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.39 (2H, t, J=7.4Hz), 4.64-4.68 (2H, m), 7.18-7.20 (1 H, m), 7.34-7.52 (6H, m), 7.55-7.57 (2H, m).

[Manufacturing Example 85-1-3] Biphenyl-3-yl-acetohydroximoyl chloride

[1039]

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HO N CI

[1040] To a mixture of 3-(2-nitro-ethyl)-biphenyl (380 mg, 1.7 mmol) described in Manufacturing Example 85-1-2 and methanol (6 mL) was added lithium methanols (130 mL), 3.4 mmol) at room temperature, which was stirred for 5 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure. A mixture of methylene chloride (7 mL) and tetrahydrofuran (3.5 mL) was added to the resulting residue at room temperature, and intainum (N) chloride (410 mL). 3.7 mmol) was added at -78°C to the reaction mixture at 7-8°C, which was stirred for 60 minutes at 0°C. The reaction mixture at making the mixture is a stirred for 60 minutes at 0°C. The reaction mixture the mixture. The organic layer was washed successively with water, saturated acqueous sodium hydrogenechomate solution and saturated aqueous sodium of thoride, and the organic layer was dried over magnesium suifate, and then filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (420 mg) as raw product. This compound was used in the subsequent reaction without further purification.

5 [Example 86] 3-(3-(4-Phenoxymethyl-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1041]

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[1042] To a tetrahydrotruran (2 m.l.) solution of 4-phenoxymethyl-phenyl-acetohydroximoyl chioride (150 mg. 0.548 mmol) described in Manufacturing Example 86-1-5 and 3-ethynyl-pyridin-2-ylamine (41 mg. 0.348 mmol) described in Manufacturing Example 1-2-2 was added thethylamine (104 µL, 0.747 mmol), which was stirred for 2 hours at 50°C. Water was added to the reaction solution at room temperature, which was then extracted with eithyl acetate. The organic layer was washed with water and saturated quieous sodium chloride and dried over anhydrous magnetism suffate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatoraphy (hepstane: evithy acetate = 41:1-2:1) to admit the till compound (39 mg. 20°A).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 4.07 (2H, s), 5.05 (2H, s), 5.39 (2H, brs), 6.25 (1 H, s), 6.70-6.73 (1 H, m), 6.95-6.98 (3H, m), 7.29-7.32 (4H, m), 7.41-7.43 (2H, m), 7.69-7.72 (1 H, m), 8.13-8.15 (1H, m)

[1043] The starting material, (4-phenoxymethyl-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 86-1-1] 1-Bromo-4-phenoxymethyl-benzene

[1044]

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[1045] To an N,N-dimethylformamide (50 mL) solution of 4-bromobenzyl bromide (5 g, 20 mmol) and phenol (2.26 g,

24 mmol) was added potassium carbonate (8.29 g, 60 mmol). This mixture was stirred for 1 hour at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium suffate, and filtered. The filtrate was concentrated under a reduced pressure, and the recidue was purified by NH-silica gel column chromatography (heptane: eithyl acetate = 4:1) to obtain the title compound (4.68

1H-NMR Spectrum (CDCl_s) δ (ppm): 5.02 (2H, s), 6.94-6.99 (3H, m), 7.27-7.33 (4H, m), 7.49-7.52 (2H, m).

[Manufacturing Example 86-1-2] 4-Phenoxymethyl-benzaldehyde

[1046]

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[1047] To a tetrahydrduran solution (50 mL) of 1-bromo-4-phenoxymethyl-benzene (4.69 g, 17.8 mmol) described in Manufacturing Example 86-11 was added dropwise n-budy lithium (1.6 ii mL 1.50 M hazene solution, 26.7 mmol) at 78°C. After 40 minutes of stirring at 78°C, N-formylmorpholine (2.25 g, 19.6 mmol) was added to this mixture, which was then stirred for a further 30 minutes at that temperature. This mixture was perfationed into lethyl either and water. The organic layer was separated washed with saturated aqueous sodium chloride, did over anhydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.8 g). This compound was used in the subsequent reaction without purification.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.16 (2H, s), 6.96-6.99 (3H, m), 7.29-7.33 (2H, m), 7.60-7.62 (2H, m), 7.90-7.92 (2H, m). 10.0 (1 H, s).

[Manufacturing Example 86-1-3] 1-((E)-2-Nitro-vinyl)-4-phenoxymethyl-benzene

[1048]

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[1049] A mixture of 4-phenoxymethyl-benzaldehyde described in Manufacturing Example 86-1-2 (3.8 g. 17.8 mmol), nitromethane (4.79 ml., 89 mmol), ammonium acetate (2.74 g. 3.6.6 mmol) and aceta acid (38 ml.) was stirred for 3 hours at 100°C. This mixture was cooled to room temperature, concentrated under a reduced pressure, and diluted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magneatum sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (4.1 g).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.13 (2H, s), 6.96-7.01 (4H, m), 7.29-7.33 (2H, m), 7.52-7.62 (4H, m), 8.00-8.03 (1 H, m).

[Manufacturing Example 86-1-4] 1-(2-Nitro-ethyl)-4-phenoxymethyl-benzene

[1050]

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[1051] To an acetic acid (4.1 mL) and dimethyl sulfoxide (70 mL) solution of 1-((E)-2-nitro-vinyl)-4-phenoxymethylbenzene (4.1 g, 16.2 mmol) described in Manufacturing Example 86-1-3 was added sodium borohydride (981 mg, 25.9 mmol) at room temperature while cooling appropriately. This mixture was stirred for 1 hour at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtened. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 4:1) to obtain the title compound (2.11 g.

¹H-NMR Spectrum (DMSO-d₆) & (ppm): 3.21-3.24 (2H, m), 4.83-4.87 (2H, m), 5.06 (2H, s), 6.91-6.95 (1 H, m), 6.98-7.01 (2H, m), 7.27-7.31 (4H, m), 7.38-7.40 (2H, m).

[Manufacturing Example 86-1-5] (4-Phenoxymethyl-phenyl)-acetohydroximoyl chloride

[1052]

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2 [183] To a methanol solution (12 mL) of 1-(2-ritro-ethyl)-4-phenoxymethyl-benzene described in Manufacturing Example 88-1-4 (1 g. 3.88 mmol) was added ithin methoxide (256 mg. 7.78 mmol). This micture was stirred for 1 house to contemperature. The mixture was concentrated under a reduced pressure, water in the residue was azeotropically distilled with toluene, and that residue was adjusted with methylene chloride (16 mL) and tetrahydrofuran (8 mL). This was cooled to 78°C, and training (10) stereochiolode (840 µL, 8.56 mmol) was added dropvise into the suspension. The mixture was stirred for 1.5 hours at room temperature. This mixture was cooled to 78°C, and partitioned into ethyl acetate and loe water. The organic layer was separated, washed with saturated aqueous sodium chioride, died over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the stille compound (10; 10; This compound (10; 1). This compound was used in the subsequent reaction without further purification.

[Example 87] 3-(3-(3-Fluoro-4-(pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1054]

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[1055] To a methanol (20.0 mL) solution of 2(2-fluro-st-Q-nitro-ethyl)-phenoxy)pyridine (600 mg, 1.81 mmo) described in Naundacturing Example 67-13 was added lithium methoxide (137 mg, 8.61 mmol) under nitrogen emosphere at room temperature, which was stirred for 30 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure, and anhydrous dichoremethane (15.0 mL) and anhydrous testrahydrofuran (7.00 mL) were added to the residue. Titanium (IV) chloride (656 µL, 5.97 mmol) was added dropvise into the reaction mixture on a dry Ice-ethanol bath (78°C), which was stirred for 30 minutes at that temperature. Sodium hydrogeneorborate and exityre lacetate were added to the reaction mixture on an Ice cooling (0°C), which was then filtered through a Cellie pad. The organic layer of the filtrate was extracted with ethyl acetate, and that organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure to obtain a crude product (300 mg). To a tetrahydrofuran (500 mL) solution of this crude product (150 mg) and 3-ctlynylpyridin-2-ylemine (300 mg, 0.254 mmol) described in Mauritacturing Example 1-23 was added triethylamine (106 pL, 0.782 mmol) at room temperature, which was stirred for 30 minutes at 50°C. Water was added to the reaction solution at room temperature, which was stirred for 30 minutes at 50°C.

acetate: heptane = 1:1), the mixture was further purified by reverse-phase high-performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1% trifluoracetic acid) to obtain the title compound (6.9 mg, 4.49%) as a dirifiltuoracetic acid still.

MS m/e(ESI) 377.15(MH+)

[1056] The starting material, 2-(2-fluoro-4-(2-nitro-ethyl)-phenoxy) pyridine, was synthesized as follows.

[Manufacturing Example 87-1-1] 3-Fluoro-4-(pyridin-2-vlmethoxy)-benzaldehyde

[1057]

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[1058] To an N,N-dimethylformamide (40.0 mL) solution of 2-(hydroxymethyl)-pyridine (3.00, 2.7.5 mmol) was added sodium hydride (1.00 g, 25.0 mmol) was added sodium hydride (1.00 g, 25.0 mmol) was then added at 0°C, and stirred for 20 minutes at room temperature. Alter was added to the reaction solution at room temperature, which was three divided the time to the macrostic with eithyl sociate. The organic layer was weaked with saturated adjuceus ostium chioride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: heptane = 1:1 → 2:11 to obtain the title compound (2.90 a. 45.60.).

1H-NMR Spectrum (CDCl₃) δ (ppm): 5.36 (2H, s), 7.15 (1 H, t, J=8.0Hz), 7.26-7.29 (1 H, m), 7.55-7.67 (3H, m), 7.74-7.78 (1 H, m), 8.61-8.63 (1 H, m), 9.86-9.87 (1H, m).

[Manufacturing Example 87-1-2] 2-(2-Fluoro-4-((E)-2-nitro-vinyl)-phenoxymethyl)-pyridine

[1059]

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ozn.

[1660] To an acetic acid (25.0 mL) solution of 3-fluoro-4-(pyridin-2-yimethoxy)-benzaldehyde (2.80 g, 12.1 mno) described in Manufacturing Example 37-1-1 were added nitromethane (8.69 g, 60.5 mno) and armonolum acetate (1.87 g, 24.2 mno) under nitrogen attempshere at room temperature, which was stirred for 2 hours at 110°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was vertracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (9.00 g) as a crude product.

14-NMR Spectrum (DMSO-Q₆) S(ppm); 5.53 (2H, s), 7.34-7.40 (2H, s), 7.54-6.84 (H, d, J=8.0Hz), 7.67 (

(Manufacturing Example 87-1-3) 2-(2-Fluoro-4-(2-nitro-ethyl)-phenoxymethyl) pyridine

[1061]

10 [1682] To a dimethyl sutfoxice (30.0 m.l.) solution of 2-(2-fluoro-4-(E)-2-nitro-vinyl)-phenocymethyl-pyridine (30.0 g. 10.9 mmol) described in Manufacturing Example 87-1-2 and acetic acid (3.00 m.l.) was added sodium borohydride (860 m.g. 17.4 mmol) at room temperature while cooling appropriately under nitrogen attimosphere, which was stirred for 20 minutes at room temperature. Water was then added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with eithy lacetate, and the organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was crystalfized with a tetrahydrofuran-ethyl acetate-heptane system and filtered to obtain the title compound (1,50 q. 48,8%).

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.18 (2H, t, J=6.8Hz), 4.84 (2H, t, J=6.8Hz), 5.50 (2H, s), 7.06-7.08 (2H, m), 7.28-7.31 (1 H, m), 7.65-7.69 (1 H, m), 7.88 (1 H, d, J=8.0Hz), 8.23-8.27 (1 H, m), 8.76 (1 H, J=5.6Hz).

[Example 88] 3-(3-(4-(Thiazol-2-vlmethoxy)-benzyl)-isoxazol-5-vl)-pyridin-2-vlamine

[1063]

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[1044] To 4-(5-(2-amino-pyridin-3-yl-)is-oxazol-3-yl-methyl-phenol (50.0 mg, 0.19 mmol) described in Manufacturing 2 Example 5-11 were added tetrahydrofuran (3 mL) and a 5N aqueous sodium hydroxide solution (37.3 µL, 0.19 mmol), which was dissolved by irradiating ultrasonic wave for 1 minue. The reaction mixture was then concentrated under a reduced pressure to obtain a white solid. An N,N-dimethyllomannide (1 mL), solution of 2-chloromethy-thiazole (28.8 mg, 0.22 mmol) described in Manufacturing Example 881-12 was added to a suspension of this solid and N,N-dimethyllomannide (2 mL), which was stirred for 1 hour at 60°C. This mixture was cooled to room temperature, and partitioned into water and ethyl acetate. The organic leyer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 1:1) to obtain the title compound (3.0 mg, 78%).

1H-NMR Spectrum (DMSO-d₄) & (ppm): 3.97 (2H, s), 5.42 (2H, s), 6.25 (2H, brs), 6.68-6.71 (1 H, m), 6.79 (1 H, s), 7.03 (2H, d, J=8.8Hz), 7.27 (2H, d, J=8.8Hz), 7.77 (1H, d, J=3.2Hz), 7.85 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 7.85-7.88 (1 H, m), 8.08 (1 H, d, J=3.2Hz), 8.08 (1 H, d, J=3.2Hz

[1065] The starting material, 2-chloromethyl-thiazole, was synthesized as follows.

[Manufacturing Example 88-1-1] Thiazole-2-yl-methanol

[1066]

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[1067] To a mixture of 2-formythiazole (300 mg, 2.65 mmol) and methanol (30 mL) was added sodium borohydride (2010 mg, 5.30 mmol) at 0°C, which was stirred for 1 hour at room temperature. Water was added to this reaction mixture, which was then extracted with eithyl sectiate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (diethyl ether) to obtain the title compound (551 zm 8.7%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 4.74 (2H, d, J=6.0Hz), 6.04 (1 H, t, J=6.0Hz), 7.63-7.65 (1 H, m), 7.73-7.75 (1 H. m).

Manufacturing Example 88-1-212-Chloromethyl-thiazole

[1068]

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CI CI

[1069] To a mixture of thiazole-2-yl-methanol (251 mg, 2.18 mmol) described in Manufacturing Example 88-1-1 and dichloromethane (10 mL) was added thionyl chloride (191 µL, 2.62 mmol) at room temperature, which was stirred for 30 minutes. Suturated aqueues sodium hydrogenechronate solution was added to the reaction mixture, which was then extracted with dichloromethane. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (20.25 m.g. 78%).

25 ¹H-NMR Spectrum (DMSO-d_e) δ (ppm); 5.11 (2H, s), 7.81-7.83 (2H, m).

[Example 89] 3-(3-(6-(3, 4-Difluoro-benzyloxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1070]

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[1071] The title compound (23 mg, 17%) was obtained according to the methods similar to those of Example 3 using 9 3-ethymyl-pyridin-2-yl-painine (40 mg, 0.3 mmol) described in Manufacturing Example 1-2-3 and (6:(3.4-difluoro-benzy-loxy)-pyridin-3-yl-paetohyr/boximoly chloride (21 mg, 0.88 mmol) described in Manufacturing Example 89-1-1.
1H-NMR Spectrum (DMSO-d₀) 8 (ppm) 4-01 (2H, s), 5.22 (2H, s), 6.27 (2H, brs), 6.70 (1 H, did, J=2,0.4.8, 8.0Hz), 6.80 (1 H, d.) 4-8.8 (1 H, m), 7.49-7.56 (1 H, m), 7.89-7.73 (1 H, m), 7.57-7.8 (1 H, m), 8.08-8.12 (1 H, m), 8.17 (1 H, s).

45 [1072] The starting material, (6-(3, 4-diffuoro-benzyloxy)-pyridin-3-yl)-acetohydroximoyl chloride was synthesized as follows.

[Manufacturing Example 89-1-1] (6-(3, 4-Difluoro-benzyloxy)-pyridin-3-yl)-acetohydroximoyl chloride

0 [1073]

[1074] The title compound (810 mg) was obtained according to the methods similar to those of Manufacturing Examples 12-1-1 through 12-1-5 using 3.4-diffuoro-benzyl alcohol.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.80 (2H, s), 5.32 (2H, s), 6.89 (1 H, d, J=8.0Hz), 7.29-7.34 (1 H, m), 7.40-7.49 (1 H, m), 7.50-7.57 (1 H, m), 7.62 (1 H, d, J=8.0Hz), 8.08 (1 H, s), 11.76 (1 H, s).

[Example 90] 3-(3-(6-(2,4-Difluoro-benzyloxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1075]

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[1076] The title compound (45 mg, 34%) was obtained according to the methods similar to those of Example 3 using 3-ethynyl-pyridin-2-ylamine (40 mg, 0.34 mmol) described in Manufacturing Example 1-2-3 and (6:(2.4-difluoro-benzy-loxyl-pyridin-3-yl-)-acetohydroximoyl chloride (210 mg, 0.68 mmol) described in Manufacturing Example 90-1-1.

"h+NMR Spectrum (DNSO-d₃) 6 (ppm): 4.01 (2H. 1, m), 7.65 (7.38 (1H. m), 7.57 (1H. dd, J=4.8, 6.012), 6.84 (1H. m), 7.58 (1H. d, J=4.08, 6.012), 6.84 (1H. m), 7.57 (1H. dd, J=4.8, 6.012), 6.84 (

[1077] The starting material, (6-(2,4-diffuoro-benzyloxy)-pyridin-3-yl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 90-1-1] (6-(2,4-Difluoro-benzyloxy)-pyridin-3-yl)-acetohydroximoyl chloride

[1078]

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[1079] The title compound (600 mg) was obtained according to the methods similar to those of Manufacturing Examples 12-1-1 through 12-1-5 using 2,4-diffuoro-benzyl alcohol.

 1 H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.80 (2H, s), 5.34 (2H, s), 6.86 (1 H, d, J=8.0Hz), 7.08-7.14 (1 H, m), 7.26-7.33 (1 H, m), 7.58 (2H, m), 8.09 (1 H, s), 11.75 (1H, s).

[Example 91] 3-(3-(5-(4-Fluoro-phenoxy)-thiophen-2-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1080]

[1081] To a tetrahydrofuran (5.00 mL) solution of (5-(4-fluoro-phenoxy)-thiophen-2-yl)-acetohydroximoyl chloride (250 mg, 0.875 mmol) described in Manufacturing Example 91-1-4 and 3-ethynyl-pyridin-2-ylamine (50.0 mg, 0.423 mmol)

described in Manufacturing Example 1-2-3 was added triethylamine (177 μ L, 1.27 mmol) at room temperature, which was stirred for 30 minutes at 60°C. Water was added to the reaction solution at room temperature, which was then extracted with extra deal wine 1941 acetale. The organic layer was weekend with saturated aqueous sodium choridre and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = $1: 2 \rightarrow 1: 1$) to obtain the title compound (11.2 mg, 721%).

¹H·NMR Spectrum (DMSO-d₆) δ (ppm): 4.17 (2H, s), 6.28 (2H, brs), 6.53 (1H, d, J=4.0Hz), 6.69-6.73 (1 H, m), 6.78 (1 H, d, J=4.0Hz), 6.88 (1 H, s), 7.13-7.17 (2H, m), 7.20-7.25 (2H, m), 7.88-7.91 (1 H, m), 8.09-8.11 (1 H, m).

[1082] The starting material, (5-(4-fluoro-phenoxy)-thiophen-2-yf)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 91-1-115-(4-Fluoro-phenoxy)-thiophene-2-carbonitrile

[1083]

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[1084] To a dimethyl sultoxide (100 mL) solution of 5-mitro-2-thiophene carbonitrile (5.00 g, 32.4 mmol) were added "Allcorphene (3.64 g, 4.8.8 mmol) and potassium carbonate (11.2 g, 8.1.0 mmol) under introgen atmosphere, which was stirred for 16 hours at 60°C. The reaction solution was cooled to room temperature and water was added, followed by particularly with eithyl acetate. The organic layer was weshed with saturated aqueue socialum chloride, and the solvent was eveporated under a reduced pressure. The residue was purified by NH silicia gel column chromatography (ethyl acetate: hearton a ± 1.0 a ± 1.5 to obtain the title compount (6.10 p. 8.6 %%).

1H-NMR Spectrum (CDCl₂) δ (ppm): 6.40 (1H, d, J=4.4Hz), 7.07-7.16 (4H, m), 7.36 (1 H, d, J=4.4Hz).

30 [Manufacturing Example 91-1-2] 5-(4-Fluoro-phenoxy)-thiophene-2-carbaldehyde

[1085]

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[1086] To a tetrahydrofuran (150 mL) solution of 5-(4-fluoro-phenoxy)-thiophene-2-carbontirie (6.10 g. 27.8 mnol) described in Manufacturing Example 91-1-1 was added dropwise dilacubyt aluminum hydride (9.3 PM h-pexane-solution, 43.0 mL, 41.7 mmol) on a dry ice-ethanol bath (-78°C) under nitrogen atmosphere, which was stirred for 2 hours at room temperature. The reaction solution was added to water, followed by extraction with ethyl acetate. The organic layer was washed with saturated squeous sodium chioride, and the solvent was eveporated under a reduced pressure. The residue was purified by silica gel column chromatography (athyl acetate: heptane = 1:5) to obtain the title compound (3.4 g. 55.0%).

 1 H-NMR Spectrum (CDCl₃) δ (ppm): 6.48-6.49 (1H, m), 7.08-7.12 (2H, m), 7.16-7.19 (2H, m), 7.52-7.54 (1 H, m), 9.71 (1 H, s).

[Manufacturing Example 91-1-3] 2-(4-Fluoro-phenoxy)-5-(2-nitro-ethyl)-thiophene

[1087]

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[1088] To an aceiic acid (20.0 m.l.) solution of 5-(4-fluoro-phenoxy)-thiophene-2-carbaldehyde (2.60 g, 11.7 mmol) described in Manufacturing Example 91-12-were added nitromethane (5.7 g, 8.5 mmol) and ammonium acetate (1.80 g, 23.4 mmol) under nitrogen atmosphere at room temperature, which was stirred for 4 hours at 110°C. Water and ethyl acetate were added to the reaction motivate, and the organic layer was extracted with ethyl acetate. This organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sutlate, and filtered. The filtrate was concentrated under a reduced pressure to obtain a crude product (3.00 g). To a dimethyl suffoxide (30.0 m.l) solution of this crude product (3.00 g) and aceitace aid (3.00 m.l) was added sodium bondyridie (6.84 g. 1.8 t mol) at room temperature while cooling appropriately, which was stirred for 20 minutes at room temperature. Water was then added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride, effect dover anhydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica et column chloridae. Find we was purified by NH silica et column chloridae. Find we was purified by NH silica et column chloridae.

H-NMR Spectrum (DMSO-d₆) 5 (ppm): 3.34 (2H, t, J=6.8Hz), 4.82 (2H, t, J=6.4Hz), 6.50 (1 H, d, J=3.6Hz), 6.69-6.71 (1 H, m), 7.12-7.16 (2H, m), 7.21-7.26 (2H, m).

[Manufacturing Example 91-1-4] (5-(4-Fluoro-phenoxy)-thiophen-2-yl)-acetohydroximoyl chloride

25 [1089]

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[1090] To a methanol (20.0 mL) solution of 2-(4-fluoro-phenoxy)-6-(2-nitro-sthy)-fltiophene (500 mg. 1.87 mmo)) described in Manufacturing Example 91-1-9 was added lithum methoxide (142 mg. 3.74 mmo) under nitrogen atmosphere at room temperature, which was stirred for 50 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure, and anhydrous dichloromethane (10.0 ml) and anhydrous fetrahydrofuran (5.00 mL) were added to the residue. Tilanium (10/ brinde (614 µL, 4.68 mmo) was added drophysis in the reaction mixture on a dry ise-ethanal bath (-78°C), which was stirred for 30 minutes at room temperature. Water, ethyl acetate and tetrahydrofuran were added to the reaction mixture on an ice cooling (0°C), and the organic layer was extracted with ethyl acetate. This organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated from the filtrate under a reduced pressure to obtain the title compound (500 mg. 3.8%) as a crude product.

¹H-NMR Spectrum (DMSO-d_c) δ (ppm): 3.95 (2H, s), 6.52 (1 H, d, J=4.0Hz), 6.76 (1 H, d, J=4.0Hz), 7.14-7.26 (4H, m), 11.82 (1 H, s).

[Example 92] 3-(3-(5-(4-Methyl-benzyl)-thiophen-2-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1091]

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[1982] To a tetrahydrofuran (5.00 mL) solution of (5-(4-methyl-benzyl)-tilophen-2-yl)-acetohydroximoyl chloridae (250 mg, 0.884 mmg) described in Manufacturing Example 92-1-5 and 9-thyrnyl-pryinde-2-yl-parine (6.00 mg, 0.423 mmg) described in Manufacturing Example 1-2-3 was added tinely almine (177 µL, 1.27 mmg) at room temperature, which was stirred for 2 hours at 80°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acceted. The organic layer was washed with saturated aqueous sodium chloride and dired over anhydrous magnesium sulfate, and the solvent was ecaporated under a reduced pressure. The residue was purified by NH 1819 electromatography (eithyl acetate: heptane = 1: 3 = 1: 2) to obtain the title compound (27.7 mg, 18.1%). 11-MNR Spectrum (DMSO-dg) 8 (ppm): 226 (3H, s), 4.02 (2H, s), 4.15 (2H, s), 6.26 (2H, brs), 6.86-6.72 (2H, m), 6.84 (H s), 7.08-7.14 (4H, m), 7.88 (H t), 6d, 2-20, 7.84H2, 8.09 (H, dd, 2-20, As (14.16)). [1033] The starting material, (5-(4-methyl-benzyl)-6-thiophen-2-yl)-acetohydroximoyl chloride, was synthesized as follows:

[Manufacturing Example 92-1-1] (5-Bromo-thiophen-2-yl)-p-tolyl-methanol

15 [1094]

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28 [195] To an anhydrous tetrahydroturen (70.0 mL) solution of 2.5-dibromothiophene (5.00 g, 19.6 mmol) was added dropwise n-buyl lithium (2.55 M n-hexane solution, 7.69 mL, 19.6 mmol) on a dry loc-ethanol bath (-78°C) under nitrogen atmosphere, which was strend for 20 minutes at -78°C. p-Tolaidehyde (2.35 g, 19.6 mmol) was then added dropwise and stirred for 10 minutes at -78°C. The reaction mixture was allowed to room temperature and water was added, followed by attraction with eithy lacetate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:5 - 1:1) to obtain the tils compound (4.30 g, 77.5%).
1H-NNR Socretum (OCDL) & foom: 2.34 (3H. s). 282 (1H. bs). 5.84 (1H. d. J. 44.0Hz). 6.56-6.57 (1H. m), 6.84 (1H. d. Socretum (CDL) & 5.00 mis 2.34 (3H. s).

35 [Manufacturing Example 92-1-2] 5-(4-Methyl-benzyl)-thiophene-2-carbaldehyde

d, J=4.0Hz), 7.15-7.17 (2H, m), 7.25-7.27 (2H, m).

[1096]

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1097] To an acatonitril (8.0.0 m.l.) solution of sodium lodied (11.4.g. 78.0 mmol) was added dropwise chlorothinethpislaine (9.6.8 m.l., 7.6.0 mmol) under nitrogen attomosphere, which was settired for 1.5 hours at room temperature. The reaction solution was cooled to -30°C, and an acatonitrile (10.0 m.l.) solution of (5-bromethiophene -2-yi)-p-toly-methand (4.0.0 g. 1.5.2 mmol) described in Manufacturing Example 92-1-1 was added dropwise and stirred for 1.5 hours at room temperature. Water was added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was exportated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: heptane = 1.10) to obtain a mixture (4.3.0 g). To a tetrahydrofuran (40.0 m.l.) solution of this mixture (2.3.0 g) was added dropwise n-butyl limium (1.5.7 M n-hoxane solution, 6.3.3 m.l., 9.47 mmol) on a dry ice-ethanol bank (7.9°C), with one sattered for 5 minutes at 7.8°C. N-diretthylformamide (864 µL, 11.2 mmol) was then added dropwise at 7.8°C, and stirred for 5 minutes at 7.8°C. The reaction solution was allowed to room temperature and water twas added, followed by extraction with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. compound (1.05 g, 56.4%).

¹H-NMR Spectrum (CDCl₃) ô (ppm): 2.33 (3H, s), 4.14 (2H, s), 6.89 (1 H, d, J=3.6Hz), 7.13 (4H, s), 7.59 (1 H, d, J=3.6Hz), 9.79(1 H, s).

5 [Manufacturing Example 92-1-3] 2-(4-Methyl-benzyl)-5-((E)-2-nitro-vinyl)-thiophene

[1098]

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[1099] To an acetic acid (10.0 m.l.) solution of 5-(4-methyl-benzyl)-thiophene-2-carbaidehyde (1.05 g, 4.85 mmol) described in Manufacturing Exemple 91-1-2 were added nitromethane (1.48 g, 24.3 mmol) and ammonium acetate (748 mg, 9.70 mmol) under nitrogen atmosphere at room temperature, which was stirred for 4 hours at 110°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was extracted with eithyl acetate. The organic layer was extracted with eithyl acetate. The organic layer was extracted with either as adsurated aqueous sodium chloride, died over anityrous magnesium suitled, and filtered. The filtrate was concentrated under a reduced pressure to obtain the filte compound (1.20 g) as a crude product. 1H-NMR Spectrum (DMSO-Qd) 5 (ppm; 227 (Hs), 4, 145 (Hs), 7, 7.4 (1 H, d, J=3.6Hz), 7.14-7.18 (HH, m), 7.66 (1 H, d. J=3.6Hz), 33 (Ht, d. J=1.32Hz), 227 (Ht, d. J=1.32Hz).

25 [Manufacturing Example 92-1-4] 2-(4-Methyl-benzyl)-5-(2-nitro-ethyl)-thiophene

[1100]

[1101] To a dimethyl sulfoxide (20.0 mL) solution of 2-(4-methyl-benzyl)-5-((E)-2-nitro-vinyl)-thiophene (1.20 g. 4.63 mmol) described in Manufacturing Example 92-1-3 and sectic acid (1.20 mL) was added sodium borohydride (280 mg. 7.41 mmol) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 20 minutes at room temperature. Water was then added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with eithyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was crystalized with a tetrahydrofuran-ethyl acetate-heptane system and filtered to obtain the title compound (625 mg, 43.45%).

¹H-NMR Spectrum (DMSO-d₆) & (ppm): 2.26 (3H, s), 3.33 (2H, t, J=6.4Hz), 4.01 (2H, s), 4.78 (2H, t, J=6.4Hz), 6.68-6.69 (1 H, m), 6.72-6.73 (1 H, m), 7.11 (4H, s).

[Manufacturing Example 92-1-5] (5-(4-Methyl-benzyl)-thiophen-2-yl)acetohydroximoyl chloride

[1102]

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[1103] To a methanol (20.0 mL) solution of 2-(4-methyl-benzyl)-5-(2-nitro-ethyl)-thiophene described in Manufacturing

Example 92-1-4 (825 mg, 2.01 mmol) was added lithium methodide (153 mg, 4.02 mmol) under nitrogen atmosphere at room temperature, which was stimed for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure, and anhydrous dichloromethane (20.0 mL) and anhydrous tetrahydrofura (10.0 ml) were added to the residue. Titanium (IV) chloride (652 µL, 5.30 mmol) was added dropwise into the reaction mixture on a lot ce-thanol bark (70°C), which was then stirred for 30 minutes at room temperature. Water, eight placetale and tetrahydrofuran were added to the reaction mixture on an ice bath (IV°C), and the organic layer was separated. This organic layer was separated with water and saturated aqueous sodium chloride, dired over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (520 mg, 92.5%) as a crude protein.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.26 (3H, s), 3.93 (2H, s), 4.02 (2H, s), 6:71 (1H, d, J=3.2Hz), 6.78 (1 H, d, J=3.2Hz), 7.09-7.15 (4H, m), 11.76 (1H, s).

[Example 93] 3-(3-(4-(2-Pyridin-2-yl-ethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

15 [1104]

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[1105] To an enhydrous terrehydrofuran (5 mL) solution of 3-ethynyl-pyridin-2-ylemine (38 mg, 0.33 mmol) described in Menufactuning Example 1-2-2 was eaded (4-2-pyridin-2-ylemiy-)bnenyl-pacelydroxiomyor) cholidre hydrochloride (310 mg, 1.0 mmol) described in Menufacturing Example 93-1-8 under nitrogen atmosphere at room temperature. Triethyramine (0.42 mL, 3.0 mmol) was then added dropwise, and stimed for 2 hours at 60°C. The reaction mixture was partitioned into water and ethyl accetate at room temperature. The organic layer was washed with water and saturate aqueous scallum chioride and critical over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromotography (ethyl accetate) teptane 3-7 then 4-16), and the resulting crude product was further purified by silica gel thin-layer chromatography (ethyl accetate) to obtain the title compound (2.12 mg, 18%).

H-NMR Spectrum (CDCl₃) 3 (ppm): 3.00-3.16 (4H, m), 4.02 (2H, s), 5.42 (2H, brs), 6.25 (1 H, s), 6.71 (1 H, dd, J=4.8, 8.0Hz), 7.10-7.25 (6H, m), 7.55-7.60 (1H, m), 7.70 (1H, dd, J=2.0, 8.0Hz), 8.13 (1 H, dd, J=2.0, 4.8Hz), 8.56(1 H, m). [1106] The starting material, (4-(2-pyridin-2-yl-ethyl)phenyl)-acetohydroximoyl chloride hydrochloride, was synthesized as follows.

40 [Manufacturing Example 93-1-1] Diethyl 4-methoxycarbonyl benzylphosphonate

[1107]

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[1108] M

[1108] Methyl 4-(bromomethyl) benzoate (50 g, 218 mmol) and triethyl phosphite (43.5 g, 262 mmol) were mixed, stirred for 30 minutes at 100°C and then stirred for 30 minutes at 120°C. The reaction solution was evaporated under a reduced pressure (165-175°C, mmHol) to obtain the title compound (58.6 g, 49%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.24 (6H, t, J=7.2Hz), 3.20 (2H, d, J=22Hz), 3.91 (3H, s), 3.98-4.18 (4H, m), 7.38 (2H, dd, J=2.4, 8.4Hz), 7.99 (2H, J=8.4Hz).

[Manufacturing Example 93-1-2] Methyl 4-(2-pyridin-2-yl-ethylenyl) benzoate

[1109]

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[1110] Sodium hydride (0.97 g, 24.2 mmol, 60% in oil) was suspended in anhydrous letrahydrotruran (20 mL) under nitrogen atmosphere, diethyl 4-methoxycarbonyl benzylphosphonate (6.96 g, 24.2 mmol) described in Manufacturing Example 63-1-1 was added at room temperature, and methanol (0.5 mL) was added followed by 30 minutes of stirring at room temperature. Next, 2-pyridinecarboxyaldehyde (2 g, 18.7 mmol) was added at room temperature and stirred for 1 hour at room temperature. The reaction mixture was partitioned into water and ethyl acetate on an ice bath (0°C). The organic layer was washed with water and saturated equeous sodium chloride and dried over enhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by sillca gel column chromatography (ethyl acetate: heptane = 1: 9) to obtain the title compound (3.71 to 3.9%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.93 (3H, s), 7.19 (1H, dd, J=4.8, 7.6Hz), 7.27 (1H, d, J=16Hz), 7.41 (1 H, d, J=7.6Hz), 7.63 (2H, d, J=8.8Hz), 7.66 (1 H, d, J=16Hz), 7.69 (1 H, t, J=8.0Hz), 8.05 (2H, d, J=8.8Hz), 8.63 (1 H, d, J=4.8Hz).

[Manufacturing Example 93-1-3] Methyl 4-(2-pyridin-2-yl-ethyl) benzoate

[1111]

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[1112] To an anhydrous tetrahydrofuran (25 mL) solution of methyl 4-(2-pyridin-2-yy-ethylenyl) benzoate (3.71 g, 15.5 mmol) described in Manufacturing Exemple 39-1-2 was added 10% palladium-carbon (50% hydrata, 1 g), which was stirred under hydrogen atmosphere for 2 hours at room temperature. The reaction mixture was filtered, and the filtrate was concentrated under a reduced pressure to obtain the title compound (3.71 g, 99%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.11 (4H, m), 3.90 (3H, s), 7.04 (1 H, d, J=7.6Hz), 7.12 (1 H, dd, J=6.0, 7.6Hz), 7.24 (2H, d, J=8.4Hz), 7.55 (1 H, t, J=7.6Hz), 7.94 (2H, d, J=8.4Hz), 8.56 (1 H, d, J=6.0Hz).

[Manufacturing Example 93-1-4] 4-(2-Pyridin-2-yl-ethyl) benzyl alcohol

[1113]

[1114] To an anhydrous tetrahydrofuran (50 ml.) solution of methyl 4-(2-pyridin-2-yl-ethyl) benzoate (3.71 g, 15.4 mmol) described in Manufacturing Example 93-1-3 was added dissobutyl aluminum hydride (0.97 M tobuene solution, 93,7 ml., 38.5 mmol on a dry te-enhanol bath (7-8°C) under nitropen atmosphere. Alter 30 minutes of striring.)

acueous potassium sodium tartrate solution (100 mL) was added to the reaction mixture, and stirred for 30 minutes at room temperature. Ethyl acetale (100 mL) was added, and the organic layer and water layer were separated. The organic layer was washed with water and saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evacorated under a reduced oressure to obtain the title compound (3.16 a. 98%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.79 (1 H, brs), 3.07 (4H, m), 4.66 (2H, s), 7.07 (1H, d, J=7.6Hz), 7.12 (1H, dd, J=6.0, 7.6Hz), 7.19 (2H, d, J=8.0Hz), 7.28 (2H, d, J=8.0Hz), 7.57 (1 H, t, J=7.6Hz), 8.56 (1 H, d, J=6.0Hz).

[Manufacturing Example 93-1-5] 4-(2-Pyridin-2-yl-ethyl) benzaldehyde

[1115]

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[1116] To an ethyl scetate (100 ml.) solution of 4-(2-pyridin-2-y-ethyl) benzyl alcohol (3.16 g. 14.8 mmo) described in Manufacturing Example 93-14 was added activated manganese dioxide (45 g. 5.18 mmo), which was sirred for 4 hours at room temperature. The reaction mixture was filtered through a Ceilite pad, and washed with ethyl acetate (100 ml.). The filtrate was concentrated under a reduced pressure to obtain the tible compound (2.57 g. 82%).

¹H-NMR Spectrum (CDCl₃) & (ppm): 3.10-3.20 (4H, m), 7.07 (1H, d, J=7.6Hz), 7.12 (1 H, dd, J=6.0, 7.6Hz), 7.34 (2H, d, J=8.0Hz), 7.57 (1H, t, J=7.6Hz), 7.79 (2H, d, J=8.0Hz), 8.56 (1H, d, J=6.0Hz), 9.97 (1 H, s).

[Manufacturing Example 93-1-6] 4-(2-Pyridin-2-yl-ethyl)-((E)-2-nitro-yinyl)-benzene

[1117]

[1118] To an acetic acid (30 mL), solution of 4-(2-pyridin-2-yi-ethyf) benzaldehyde (2.57 g, 12.2 mmol) described in Manufacturing Example 93-1-5 were added nitromethane (7.45 g, 122 mmol) and ammonium acetate (1.88 g, 2.44, mmol) under nitrogen atmosphere at room temperature, which was sirred for 3 hours at 120°C. The reaction mixture was partitioned into water and ethyf acetate. The organic layer was washed with water and saturated aqueous sodium chioride and dried over anhydrous megapium sulfate, and the solvent was everporation under a reduced pressure to obtain the title compound (2.88 g, 91 %) as a rew product.

1H-NMR Spectrum (CDCl₂) & (ppm): 3.10-3.20 (4H, m), 7.07 (1H, d, J=7.6Hz), 7.12 (1 H, dd, J=6.0, 7.6Hz), 7.26 (2H, d, J=8.0Hz), 7.45 (2H, d, J=8.0Hz), 7.55 (1 H, d, J=13.6Hz), 7.57 (1 H, t, J=7.6Hz), 7.98 (1 H, d, J=13.6Hz), 8.56 (1 H, d, J=6.0Hz).

[Manufacturing Example 93-1-7] 4-(2-Pvridin-2-vl-ethyl)-(2-nitro-ethyl)-benzene

[1119]

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1120] To a mixed tetrahydrofuran-dimethyl sulfoxide (1:1) solution of 4-(2-pyridin-2-yi-ethyl-(E)-2-nitro-vinyl-benzene (2.89 g, 11.1 mmol) described in Manufacturing Example 93-1-6 and acetic acid (3 mL) was added sedium borohydride (800 mg, 16.7 mmol) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 15 minutes at room temperature. Water was added dropwise into this reaction mixture at room temperature while cooling appropriately. The reaction mixture was partitioned into water and ethyl acetale. The organic layer was season with the compound of the properation of the season of the properation of the

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.07 (2H, t, J=7.6Hz), 3.29 (2H, t, J=7.2Hz), 3.47 (2H, t, J=7.6Hz), 4.60 (2H, t, J=7.2Hz), 7.13 (2H, d, J=8.0Hz), 7.19 (2H, d, J=8.0Hz), 7.19 (1 H, d, J=7.6Hz), 7.30 (1 H, dd, J=6.0, 7.6Hz), 7.78 (1 H, t, I=7.6Hz)

[Manufacturing Example 93-1-8] (4-(2-Pyridin-2-yl-ethyl)-phenyl)-acetohydroximoyl chloride hydrochloride

[1121]

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HO N

[1122] To a methanol (30 mL) solution of 4-(2-pyidin-2-y-lethyl)-(2-nitro-ethyl)-benzene (1 g. 3.9 mmol) described in Manufacturing Example 34-17 was added lithium methoxide (296 mg, 7.8 mmol) under nitrogen atmosphere at room temperature, which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. Anhytrous methylene chloride (20 mL) and anhydrous tetrahydroturan (10 mL) were added to the residue. Trainmil (10 chloride (11 M dichloromethene solution, 12.5 mL, 12.5 mmol) was added dropybes into the reaction mixture on a dry loc-ethanol bath (7-8°C), which was stimed for 30 minutes at 0°C. Water and ethyl acetate were added to the reaction mixture on an ice bath (0°C), which was then neutralized by addition of a 10% sequences sodium hydrogencarbonate solution. The reaction liquid including precipitate was filtered through a Celite pad and washed with ethyl acetate. The organic layer was separated from the filtrate. This organic layer was washed with water and saturated aqueous sodium chloride and dried over anhydrous magnesium sultate, and the anhydrous magnesium sultate, was filtered. A 4 N hydrochloric acid-ethyl acetate solution (4 mL) was added to the filtrate, and the solvent was evaporated under a reduced pressure to total the title compound (324 mg, 100%).

¹H-NMR Spectrum (DMSO-d6) δ (ppm): 3.08 (2H, t, J=7.6Hz), 3.32 (2H, t, J=7.6Hz), 3.78 (2H, s), 7.12-7.26 (4H, m), 7.80-7.94 (2H, m), 8.43 (1 H, m), 8.80 (1 H, m).

[Example 94] 3-(3-(3-Fluoro-4-(5-fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1123]

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[1124] To a tetrahydrofuran (5.00 mL) solution of (3 fluono-4-(5-fluoro-pyriáin 2 ylmethoxy) phanyl)-acelohydroximoyl chioride (170 mg, 0.554 mmo) described in Manufacturing Example 94-1-3 and 3-ethynyl-pyridin-2-ylenine (4.00 mg, 0.399 mmo)) described in Manufacturing Example 1-2-3 was added triethylamine (142 µL, 1.02 mmo) at room temperature, which was stirred for 4 hours at room temperature. Water was added to the reaction solution at room temperature, which was then extracted with ethyl scetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:3--1:2) to obtain the title compound (18.0 mg, 13.5%).

1H-NMR Spectrum (DMSO-d₀) δ (ppm): 3.98 (2H, s), 5.23 (2H, s), 6.27 (2H, brs), 6.70 (1 H, dd, ±0.8, 8.0Hz), 6.82 (1 H, s), 7.07 (1H, d, ±0.8) ch2/y, 7.18-7.28 (2H, m), 7.61 (1 H, dd, ±0.8, 8.4Hz), 7.76-7.81 (1 H, m), 7.86-7.88 (1 H, m), 8.09 (1 H, dd, ±0.16, 8.48Hz), 5.86-8.59 (1 H, m),

[1125] The starting material, (3 fluoro-4-(5-fluoro-pyridin-2-ylmethoxy)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

25 [Manufacturing Example 94-1-1] 3-Fluoro-4-(5-fluoro-pyridin-2-ylmethoxy)-benzaldehyde

[1126]

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[1127] To an N.N-dimethytomamide (20.0 m.l.) solution of (s-fluore-pyridin-2-y)-methanol (760 mg, 5.98 mmol) described in Manufacturing Exemple 41-1.1 was added sodium hydride (239 mg, 5.98 mmol, 60% in oil) under nitrogen atmosphere at 0°C, which was stirred for 10 minutes at room temperature. 3-4-Dilluorobenzaldehyde (385 mg, 5.85 mmol) was then added at room temperature, and stirred for 30 minutes at room temperature. Water was added to the reaction solution at room temperature, which wish then extracted. The origin is layer was avaished with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silica get column chromatography (ethy lacetate: helptane = 1.3) to obtain the title compound (629 mg, 42.25%). 45 H-NMR Spectrum (CDCl₃) δ (ppm): 5.33 (2H, s), 7.15 (1H, t, J=8.0Hz), 7.45-7.50 (1 H, m), 7.57-7.66(3H, m), 8.47 (1 H, d, J=2.21-2), 8.97 (1 H, d, J=2.04-12).

[Manufacturing Example 94-1-2] 5-Fluoro-2-(2-fluoro-4-(2-nitro-ethyl)-phenoxymethyl)-pyridine

50 [1128]

[1129] To an acetic acid (8.00 mL) solution of 3-fluoro-4-(5-fluoro-pyridin-2-yinethoxy)-benzaldehyde (8.29 mg. 2.82 mmg) described in Marufacturing Example (84-1-1 were added nitromethane (789 mg. 12.6 mmg)) and ammonium acetate (388 mg. 5.04 mmol) under nitrogen atmosphere at room temperature, which was stirred for 5 hours at 100°C. Water and ethyl acetate were added to the reaction solution, and the organic layer was extracted with ethyl acetate. The organic layer was exhaved with water and saturated aqueous sodium chloride, dried over anhydrous magnesium surfate, and filtered. The fiftrate was concentrated under a reduced pressure to obtain a crude product (736 mg). To a dimethyl surfoxide (10.0 mL) solution of this crude product (736 mg) and aceta cald (700 µL) was added sodium borohydride (155 mg. 4.03 mmol) at room temperature while coding appropriately, which was stirred for 30 minutes at room temperature. Water was then added dropwise at room temperature with cooling appropriately. The reaction mixture was extracted with ethyl scattae, and the organic layer was washed with water and saturated aqueous sodium chloride, dried was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1 : 5) to obtain the title compound (341 mg. 48 ft%).

¹H-NMR Spectrum (DMSO-d₆) ô (ppm): 3.16 (2H, t, J=6.8Hz), 4.83 (2H, t, J=6.8Hz), 5.22 (2H, s), 7.01-7.03 (1 H, m), 7.16-7.24 (2H, m), 7.59-7.63 (1 H, m), 7.77-7.82 (1 H, m), 8.59 (1 H, d, J=2.8Hz).

[Manufacturing Example 94-1-3] (3-Fluoro-4-(5-fluoro-pyridin-2-ylmethoxy)-phenyl)-acetohydroximovl chloride

[1130]

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HO N O N

[1131] To a methanol (20.0 m.L) solution of 5-fluoro-2-(2-fluoro-4-(2-nitro-ethyl)-phenoxymethyl)-pyridine (341 mg, 1.16 mmo) described in Manufacturing Example 94-1 was added lithium methoxide (88.1 mg, 2.32 mmol) under nitrogen atmosphere at room temperature, which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure, and anhydrous dichloromethane (20.0 mL) and anhydrous tetrahytrofuran (10.0 mL) were added to the residue. Titanium (10.0 mlc) were added to the residue. Titanium (10.0 mlc) were added to the reaction mixture on a dry loe-ethanol bath (-78°C), which was stirred for 60 minutes at room temperature. Water, ethyl acetate and tetrahydrofuran where added to the reaction mixture on an loe bath (10°C), and the organic layer was exhateded with ethyl acetate. This organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (340 mg, 93.7%) as a crude product.

1H-NMR Spectrum (DMSO-d_s) δ (ppm): 3.77 (2H, s), 5.24 (2H, s), 7.01-7.02 (1 H, m), 7.12-7.16 (1 H, m), 7.20-7.24 (1

H, m), 7.60-7.63 (1 H, m), 7.77-7.82 (1 H, m), 8.59 (1 H, d, J=2.8Hz), 11.74 (1H, s).

[Example 95] 3-(3-(2-Fluoro-4-(pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1132]

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[1133] To a methanol (2.0 ml.) solution of 2-(3-fluoro-4(2-nitro-ethyl)-phenoxymethyl)-pyridine (400 mg. 1.45 mmol) described in Manufacturing Example 95-1-3 was added lithium methoxide (110 mg. 2.90 mmol) under nitrogen atmosphere at room temperature, which was stirred for 30 minutes at room temperature. The solvent was evaporated from the reaction mixture under a reduced pressure, and anhydrous dichloromethane (2.00 mL) and anhydrous tetrahydrofuran (10.0 ml) were added to the residue. Titanium (IV) chloride (510 μ L, 4.64 mmol) was added dropwise into the reaction mixture on a dry ice-ethanol banh (78°C), which was stirred for 80 minutes at room temperature. Water, eithyl actatic and iterahydrofuran were added to the reaction mixture on an ice bath (9°C), and the organic layer was extracted with eithyl acetatic. For egranic layer was washed with water and saturated aqueous sodium chloride, dired over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain a crude product (380 mg), To a tetrahydrofuran (5.00 mg) solution of this crude product (180 mg) and 3-dhyby-pyforide-2ylamine (400 mg). 0.339 mmol) described in Manufacturing Example 1-2-3 was added to the reaction solution at more temperature, which was stirred for 1 hour at 60°C. Water was added to the reaction solution at more temperature, which was then extracted with eithyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over enhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH allica gel column chromatorpaphy (ethyl acetate: heptare = 1: 3 \rightarrow 1: 2) to obtain the title compound (25.2 mg, NH) was allicated and column thromatorpaphy (ethyl acetate: heptare = 1: 3 \rightarrow 1: 2) to obtain the title compound (25.2 mg,

¹H-NMR Spectrum (DMSO-d₆) 8 (pm): 3.98 (2H, s), 5.18 (2H, s), 6.28 (2H, brs), 6.88-6.71 (1 H, m), 6.77 (1 H, s), 6.86 (1 H, dd, J=2.4, 8.4Hz), 6.95 (1 H, dd, J=2.4, 12.0Hz), 7.29-7.37 (2H, m), 7.51 (1 H, d, J=6.0Hz), 7.82-7.88 (2H, m), 8.08-8.09 (1 H, m), 8.57-8.59 (1H, m).

[1134] The starting material, 2-(3-fluoro-4-(2-nitro-ethyl)-phenoxymethyl)-pyridine, was synthesized as follows.

[Manufacturing Example 95-1-1] 2-Fluoro-4-(pyridin-2-vlmethoxy)-benzaldehyde

[1135]

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[1136] To an NN-dimetryformamide (10.0 mL) solution of 2-fluoro-4-hydroxybonzaldichyde (1.80 g. 11.4 mmol) was added soldium hydride (547 mg, 13.7 mmol, 67% in in) under nitrogen atmosphere at 07°C, which was stirred for 30 minutes at room temperature. 2-Picotyl chloride (2.80 g, 17.1 mmol) was then added at room temperature and stirred for 10 mol at 70°C. Water was added to the reaction solution at room temperature, which was then extracted with etryl for the cate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was exportated under a reduced pressure. The residue was purified by silica gel column chromatography (etityl acetate: heptane = 1:3) to obtain the title compound (1.07 g, 4.0%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.27 (2H, s), 6.74-6.77 (1H, m), 6.87-6.90 (1H, m), 7.26-7.29 (1 H, m), 7.47-7.49 (1 H, m), 7.73-7.85(2H, m), 8.62-8.64 (1 H, m), 10.21 (1 H, s).

[Manufacturing Example 95-1-2] 2-(3-Fluoro-4-((E)-2-nitro-vinyl)-phenoxymethyl) pyridine

[1137]

[1138] To an acotic acid (15.0 mL) solution of 2-fluoro-4-(pyrdiin-2-yheriboxy)-benzaldehyde (1.07 g, 4.63 mmo) described in Manufacturing Example 95-1-1 were added nitromethane (1.41 g, 23.2 mmo) and ammonium acetate (714 mg, 9.26 mmoi) under nitrogen atmosphere at room temperature, which was stirred for 2 hours at 100°C. Water and ethy acetate were added to the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was exhanded with water and saturated acqueus sodium chloride, dried over anthydrous magnerium sulfate, and

filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.20 g) as a crude product. 'H-NMR Spectrum (DMSO-d₆) 6 (ppm): 5.30 (2H, s), 7.02-7.05 (1H, m), 7.14-7.18 (1 H, m), 7.36-7.39 (1H, m), 7.54 (1 H, d. J-s/8Hz), 7.85-7.89 (1 H, m), 7.93 (1 H, t. J-s.8Hz), 8.06 (2H, s), 8.59-8.61 (1 H, m).

5 [Manufacturing Example 95-1-3] 2-(3-Fluoro-4-(2-nitro-ethyl)-phenoxymethyl)-pyridine

[1139]

19 0 N

[1140] To a dimethyl sulfoxite (20.0 m.) solution of 2-(3-fluoro-4-((ξ)-2-hitto-vinyl)-phenoxymethylpyridine (1.20 g) described in Manufacturing Example 95-1-2 and acetic acid (1.00 mL) was added sodium borohydride (249 mg, 6.57 mmo) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 30 minutes at room temperature. Water was then added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with entily acetals, and the organic layer was vashed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, followed by cystalization with an ethylacetate-pasine system and filtration to betain the title compound (314 mg, 50.7%). 1H-NMR Spectrum (DMSO-d₀) δ (ppm): 3.21 (2H, t, J=7.2Hz), 4.79 (2H, t, J=7.2Hz), 5.46 (2H, s), 6.82 (1 H, d, J=2.4, 8.4Hz), 7.32 (1 H, t, J=8.8Hz), 7.86 (1 H, t, J=6.4Hz), 7.87 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, d, J=8.0Hz), 8.21-8.25 (1 H, m), 8.77 (1 H, m), 8.77

(Example 96) 3-(3-(2-Fluoro-4-(5-fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1141]

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(5) [1142] To a tetrahydrofuran (5.00 mL) solution of (2-fluoro-4-(5-fluoro-pyridin-2-yhnethoxy)-pheny/)-scetohydroximoyl chloride (170 mg, 0.554 mmoi) desorbed in Meundacturing Example 18-1.4 and 3-ethynyf-pyridin-2-ylamina (4.00 mg, 0.393 mmol) desorbed in Manufacturing Example 1-2-3 was added theflylamine (142 pL, 1.02 mmol) at roon temperature, which was stirred for 4 hours at room temperature. Water was added to the reaction solution at room temperature, which was then extracted with ethyl accetate. The organic layer was washed with saturated aqueous sodium chloride and dried over arhydrous magnesium sulfate, and the solvent was developerated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:3 → 1:2) to obtain the title compound (32.0 mg. 2.9 %).

1H-NMR Spectrum (DMSO- d_0) δ (ppm): 3.99 (2H, s), 5.18 (2H, s), 6.26 (2H, brs), 6.68-6.71 (1 H, m), 6.77 (1 H, s), 6.86 (1 H, dd, J=2.4, 8.412), 6.96 (1 H, dd, J=2.4, 12.0142), 7.31 (1 H, t, J=8.8142), 7.61 (1 H, dd, J=4.8, 8.812), 7.78 (1 H, dd, J=4.8, 7.8142), 7.78 (1 H, dd, J=4.8, 7.8142), 7.78 (1 H, dd, J=1.8, 7.8142), 8.09 (1 H, dd, J=1.8), 7.8142, 8.09 (1 H, dd, J=1.8), 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442, 8.1442,

[1143] The starting material, (2-fluoro-4-(5-fluoro-pyridin-2-ylmethoxy)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 96-1-1] 2-Fluoro-4-(5-fluoro-pyridin-2-ylmethoxy)-benzaldehyde

[1144]

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[1145] To an N,N-dimethylformamide (20.0 mL) solution of 2-fluoro-4-hydroxybenzaldehyde (1.48 g, 10.2 mmol) was added softlum hydride (411 mg, 10.3 mmol, 60% in fill) under nitrogen etmosphere at 0°C, which was stifred for 20 minutes at room temperature. 2-chloromethyl-5-fluoro-pyridine (1.20 g, 3.65 mmol) described in Manufacturing Example 41-1-2 was then added at room temperature, and stirred for 30 minutes at 80°C. Water was added at room temperature to the reaction solution, which was then extracted with ethyl societate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by silice all column chromosopahy (ethyl acetate: heptener = 1: 5 - 1: 2) to obtain the title compound (901 mg, 422%).

11-MMR Spectrum (CDCl₃) 6 (ppm): 5.24 (2H, s), 6.73-6.77 (1 H, m), 8.87-6.89 (1 H, m), 7.46-7.51 (2H, m), 7.84 (1 H, ±8.44%). A84 (1 H, d, ±8.44%). 10.22 (1 H, s)

[Manufacturing Example 96-1-2] 5-Fluoro-2-(3-fluoro-4-((E)-2-nitro-vinyl)-phenoxymethyl)-pyridine

[1146]

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[1147] To an acetic acid (20.0 ml.) solution of 2-fluoro-4/5-fluoro-pyridin-2-yrimethoxy)-benzaldehyde (90 mg. 3.62 mmol) described in Manufacturing Example 96-1-1 were added nitromethane (1.10 g. 18.1 mmol) and ammonium acetate (658 mg. 7.24 mmol) under nitrogen atmosphere, which was stirred for 2 hours at 110°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.00 g) as a crude product.
1H-NMR Spectrum (DMSO-Q₃) 8 (ppm); 5.30 (2H, s), 7.04 (1 H, dd, J=2.4, 8.8Hz), 7.17 (1 H, dd, J=2.4, 7.2Hz), 7.63-7.66
(1 H, m. 7.78-7.86 1 H, m.), 7.80 (1 H, d., J=8.4Hz), 8.00 (2H, s), 8.16 (1 H, d., J=8.4Hz).

[Manufacturing Example 96-1-3] 5-Fluoro-2-(3-fluoro-4-(2-nitro-ethyl)-phenoxymethyl)-pyridine

[1148]

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[1149] To a dimethyl sulloxide (20.0 m.)-terlahydrofuran (5.00 m.) solution of 5-fluoro-2-(3-fluoro-4-(6)2-2-nitro-viny)-phenoxymethyl-pyridine (1.00 g., 3.42 mmol) described in Manufacturing Example 96-1-2 and acetic acid (1.00 m.) was added sodium borohydride (207 mg., 5.47 mmol) at room temperature while cooling appropriately under nitrogen atmosphere, which was stirred for 10 minutes at room temperature. Water was then added dropwise at room temperature while cooling appropriately. The reaction mixture was extracted with effly acetate, and the organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was crystallized with an ethyl acetate: he phane system and filtered to obtain the title compound (346 mg., 34.4%).

¹H-NMR Spectrum (DMSO-d_e) ô (ppm): 3.20 (2H, t, J=6.8Hz), 4.79 (2H, t, J=6.8Hz), 5.17 (2H, s), 6.84 (1 H, dd, J=2.4, 8.4Hz), 6.94 (1 H, dd, J=2.4, 12.0Hz), 7.27 (1 H, t, J=6.8Hz), 7.61 (1 H, dd, J=4.4, 8.8Hz), 8.78 (1 H, ddd, J=2.8, 8.8, 17.6Hz), 8.59.859 (1H m).

[Manufacturing Example 96-1-4] (2-Fluoro-4-(5-fluoro-pyridin-2-ylmethoxy)-phenyl)-acetohydroximoyl chloride

5 [1150]

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[1151] To a methanol (20.0 mL) solution of 5-fluoro-2-(3-fluoro-4-(2-hitro-ethyl)-phenoxymethyl)-pyridine (246 mg. 1.18 mmol) described in Manufacturing Example 96-1-3 was added lithium methoxide (88.6 mg. 2.38 mmol) under nitrogen atmosphere at room temperature, which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure, and anhydrous dichloromethane (20.0 mL) and anhydrous tetrahydrofuran (10.0 mL) were added to the residue. Titanium (10.0 mL) were added to the residue. Titanium (10.0 mL) was added dropwise into the reaction mixture on an dry loe-ethanol bath (-78°C), which was stirred for 60 minutes at room temperature. Water, ethyl scetate and tetrahydrofuran were added to the reaction mixture on an ice bath (0°C), and the organic layer was extracted with ethyl scetate. This organic layer was washed with water and saturated aqueous sodium chloride, dred over anhydrous magnealum sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (300 mm.8 if 3%) as a crude product.

¹H-NMR Spectrum (DMSO-d₄) δ (ppm): 3.79 (2H, s), 5.19 (2H, s), 6.87 (1 H, dd, J=2.4, 8.4Hz), 6.95 (1 H, dd, J=2.8, 12.0Hz), 7.26 (1 H, t, J=8.8Hz), 7.62 (1 H, dd, J=4.4, 8.8Hz), 7.78(1 H, ddd, J=3.2, 8.8, 13.6Hz), 8.59(1 H, dd, J=0.4, 2.8Hz), 11.72(1 H, s).

[Example 97] 3-(3-(6-Phenylsulfanyl-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1152]

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[1153] To a tetrahydrofuran (5 ml.) solution of (6-phenylsulfanyl-pyridin-2-yl-)-acothydroximoyl chloride (148 mg. 0.54 mmol) described in Manufacturing Example 97-1-4 and 3-ethynyl-pyridin-2-ylamine (15 mg. 0.13 mmol) described in Manufacturing Example 12-3 was added thethylamine (80 µL, 0.57 mmol), which was stirred for 4 hours at 50°C under nitrogen atmosphere. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetals. The orusine lawer was separated, washed with saturated aqueous sodium chloride, dried over anilydrous.

magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: methanol = 10:1) and then further purified by silica gel column chromatography (ethyl acetate: methanol = 10:1) to obtain the tile compound (11 im. 23%).

1H-1MR Spectrum (CDCl₃) δ (ppm):3.99 (2H, s), 5.39 (2H, s), 6.24 (1 H, s), 7.72 (1 H, dd, J=4.8, 7.7Hz), 6.87 (1 H, d, J=8.2Hz), 7.38 (1 H, dd, J=2.4, 8.2Hz), 7.40-7.43 (3H, m), 7.58-7.60 (2H, m), 7.70 (1 H, dd, J=1.8, 7.7Hz), 8.15 (1 H, dd, J=1.8, 4.8Hz), 8.40 (1 H, d, J=2.4Hz).

[1154] The starting material, (6-phenylsulfanyl-pyridin-3-yl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 97-1-1] 5-Bromo-2-phenylsulfanyl-pyridine

[1155]

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[1156] To an N.N-dimethylformamide (20 mL) solution of thiophenol (1.02 g. 9.28 mmol) was added sodium hydride (446 mg. 9.28 mmol) 50% in 0ll, which was stirred for 15 minutes at room temperature, 25-Olbromopyridine (2.00g, 8.44 mmol) was then added to thie reaction inhiture and stirred for 35 minutes at room temperature, and then for a further 45 minutes at 55°C. Water was added to the reaction solution at room temperature, which was then extracted with ethyl accetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dired over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH sillica gel column chloromategraphy (heptans: estily adeatise: 4.11) to obtain the title compound (2.24 g. quant.). 11-N-MR Spectrum (CDCl₃) 5 (ppm):6.78 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73, 8.4Hz), 7.42-7.45 (3H, m), 7.58-7.60 (3H, m), 8.47 (1 H, dd, J=0.73,

[Manufacturing Example 97-1-2] 6-Phenylsulfanyl-pyridine-3-carbaldehyde

[1157]

[1188] To a tetrahydrofuran (40 mL) solution of 5-bronno-2-phenylsulfanyl-pyridine (2.24 g, 8.42 mmol) described in Manufacturing Example 97-1-1 was added n-bulyl lithium (6.35 mL, 1.6 M hexane solution, 10.1 mmol) under nitrogen atmosphere at - 78°C, which was attired for 45 minutes at -78°. Next, N, N-dimethylformamide (8.48 µL, 1.0,9 mmol) was added to this reaction mixture, and stirred for 35 minutes as the temperature was gradually raised to room temperature. Water was added to the reaction solution at room temperature, with was then extracted with eithy actelate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and fillered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane : ethyl acetale 2 = 11 to obtain the title compound (583 mg, 25%).

¹H-NMR Spectrum (CDCl₃) δ (ppm):6.94 (1H, d, J=8.4Hz), 7.48-7.52 (3H, m), 7.62-7.65 (2H, m), 7.89 (1 H, dd, J=2.4, 8.4Hz), 8.82 (1 H, dd, J=0.73, 2.2Hz), 9.98 (1 H, s).

55 [Manufacturing Example 97-1-3] 5-(2-Nitro-ethyl)-2-phenylsulfanyl-pyridine

[1159]

[1180] To an acetic acid (10 mL), solution of 8-phenylsulflamy-t-pyridine-3-carbatiethyde (683 mg, 2.71 mmol) described in Manufacturing Example 97-1-2 were added nitromethane (734 µL, 13.6 mmol) and ammonium acetate (418 mg, 5.42 mmol), and which was stirred for 4 hours 35 minutes at 100°C under nitrogen strussphere. Water was added to the reaction solution at room temperature, which was then extracted with ethyl acetate. The organic layer was separated, washed with seturated aqueous sodium choindry, dired over analyticus magnessim suitets, and filterof. The filtrate was concentrated under a reduced pressure. To a climethyl sulfoxide (10 mL) and acetic acid (1 mL) solution of the residue was acided solution borrybristic (205 mg, 5.42 mmol), which was stirred for 56 minutes at morn temperature. Solution hydrogencarbonate and water were added to the reaction mixture at room temperature while cooling appropriately, which was then extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium choritors, dired over anhyrous magnessim sulfate, and filtered. The fiftrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane : ethyl acetate = 1 : 1) to obtain the title corpound (212 mg, 30%).

¹H-NMR Spectrum (CDCl₃) δ (ppm):3.27 (2H, t, J=6.6Hz), 4.60 (2H, t, J=6.6Hz), 6.71 (1 H, d, J=8.6Hz), 7.39 (1 H, d, J=8.4Hz), 7.50-7.58 (3H, m), 7.62-7.64 (2H, m), 8.57 (1H,s).

25 [Manufacturing Example 97-1-4] (6-Phenylsulfanyl-pyridin-3-yl)-acetohydroximoyl chloride

[1161]

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[1162] To a methanol (5 mL) solution of 5-(2-nitro-ethyl)-2-phenylsulfanyl-pyridine (212 mg, 0.814 mmol) described in Manufacturing Example 97-1-3 was added ikhium methoxide (62 mg, 1.6 mmol), which was stirred for 5 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure, and the residue was suppended in tetrahylorduran (5 mL) and methylene chloride (3 mL). Titanium (IV) tetrachioride (197 µL, 1.8 mmol) was added to interest the suspension under a nitrogen atmosphere at 7-67°, which was stirred for 1 hour and 30 minutes at 10°C. The mixture was then stirred for another 50 minutes at 10°C norm temperature, after which water was added at 0°C to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous colum chloride, dried over anhytrous magnesium sulfate, and then fillered. The filtrate was concentrated under a reduced pressure to obtain the title compound (249 mg, quant.). This compound was used in the following reaction without any further ourification.

[Example 98] 3-(3-(4-(3-Methoxy-benzyloxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1163]

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[1164] To 4-(6-(2-amino-pyridin-3-y)-isoxazo-(3-y)methyl)-phenol (30 mg, 0.11 mmol) described in Menufacturing 52-maple 51-1 were tetrahydrufuran (3 ml) and as fix sodium hydroxide aqueous solution (22 µ µ, 0.11 mmol), which was dissolved by irradiating ultrasonic wave for 1 minute. The reaction solution was then concentrated under a reduced pressure, which gave a winke solid. To a suspension of this cool in N,N-dimethylformamide (1 ml.), was added an N,N-dimethylformamide (1 ml.) solution of 3-methocyberzyl chloride (21.0 mg, 0.13 mmol), which was stirred for 12 hours at 60°C. This mixture was cooled to room temperature and partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dired over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and this residue was purified by NH silica gel column chromatomaphy fleptates rethyl acetate 1:10 to obtain the title compound (35 1 mg, 81 %).

1H-1MRI Spectrum (DMSO-d₀) & (ppm): 3.75 (3H, s), 3.95 (2H, s), 5.05 (2H, s), 6.25 (2H, brs), 6.67-6.71 (1H, m), 6.78 (1H, s), 6.86-6.90 (1H, m), 6.96 (2H, d, J = 8.4 Hz), 6.97-7.00 (2H, m), 7.24 (2H, d, J = 8.8 Hz), 7.29 (1H, t, J = 8.0 Hz), 7.85-7.86 (1H, m), 8.07-8.10 (1H, m).

[Example 99] 3-(3-(4-(6-Methoxy-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1165]

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[1166] Tetrahydrofuran (3 mL) and a 5N sodium hydroxide aqueous solution (22.4 µL, 0.11 mmol) were added to 4-(5-(2-amino-pyridin-5y)-jeoxazo-3-yimethyl)-pienol (30 mg, 0.11 mmol) described in Manufacturing Example 5-1-1, which was deslowed by irradiating uitrasonic wave for 1 minut. The reaction solution was then connentrated under a reduced pressure, which gave a white solid. To a suspension of this solid in N.N-dimethylformamide (1 mL) was added an N.N-dimethylformamide (1 mL) solution of the 2-chloromethyl-6-methoxy-pyridine (21.2 mg, 0.13 mmol) described in Manufacturing Example 99-1-2, which was stirred for 12 hours at 60°C. This reaction mixture was cooled to room temperature and partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium-chloride, died over anhydrous magnesismus uslate, and filtered. The filtrate was concentrated under a reduced pressure, and this residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 1: 1) to obtain the title compound (38.7 mg, 48%).

1H-NMR Spectrum (DMSO-d₂) δ (ppm) : 3.85 (3H, s), 3.96 (2H, s), 5.07 (2H, s), 6.25 (2H, brs), 6.69 (1 H, dd, J = 4.8, 7.6 Hz), 6.75 (1 H, d, 8.04z), 6.79 (1 H, d), 8.6 Hz), 7.70 (1 H, d, J = 7.2 Hz), 7.25 (2H, d, J = 8.8 Hz), 7.69 7.74 (1 H, m), 7.857 -588 (1 H, m), 8.081 (H, dd, J = 2.0, 4.8 Hz).

The starting material, 2-chloromethyl-6-methoxy-pyridine, was synthesized as follows. [Manufacturing Example 99-1-1] (6-Methoxy-pyridin-2-yl)-methanol

[1167]

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[1188] To a mixture of 2-bromo-6-methoxypyridine (500 mg. 2.68 mmol) and toluene (20 mL) was added dropwise robuly lithium (1.84 mL, 1.6 M hexane solution, 2.93 mmol) at -78°C, which was stirred for 30 minutes. N,N-dirinethyl-formamice (412 µL, 5.32 mmol) was added dropwise to the mixture at the same temperature, which was stirred for 45 minutes at 0°C. Water and tetrahydrofuran were added to the reaction solution and vigorously stirred. The organic layer was separated, washed with water and saturated aqueous sodium chloride, died over anhydrous mannerum sulfate,

and filtered. Sodium borohydride (201 mg, 5.31 mmol) was added to this filtrate at 0°C, which was sirred for 2 hours at memperature. Water was added to the reaction solution, which was then exacted with ethyl acetate. The organic isyer was separated, washed with saturated aqueous sodium chloride, dried with anhydrous magnesium suitlete, and then dried. This filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatoprately hexpans: sidtleth letter 2-11 to addin the little compound (10.48 mz. 28).

¹H-NMR Spectrum (DMSO-d_g) δ (ppm) : 3.81 (3H, s), 4:47 (2H, d, J = 6.0 Hz), 5.34 (1 H, t, J = 5.6, 6.0 Hz), 6.65 (1 H, dd, J = 0.8, 8.4 Hz), 7.03-7.05 (1 H, m), 7.68 (1 H, dd, J = 7.2, 8.0 Hz).

[Manufacturing Example 99-1-2] 2-Chloromethyl-6-methoxy-pyridine

[1169]

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[1170] To a mixture of dichloromethane (5 mL) and the (6-methoxy-pyridin-2-yi)-methanol (105 mg, 0.75 mmol) described in Manufacturing Example 99-1-1 was added thionyl chloride (82.4 µL, 1.13 mmol), which was stirred for 30 minutes at room temperature. A saturated sodium hydrogencarbonate aqueous southion was added to this reaction mixture, which was then extracted with dichloromethane. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrour magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (105.8 mg, 89%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.85 (3H, s), 4.69 (2H, s), 7.79 (1 H, dd, J = 0.4, 8.4 Hz), 7.12 (1H, dd, J = 0.4, 7.2 Hz), 7.73 (1 H, dd, J = 7.2, 8.4 Hz).

[Example 100] 3-(3-(6-(Pyridin-3-vloxy)-pyridin-3-vlmethyl)-isoxazol-5-vl)-pyrindin-2-vlamine

v [1171]

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[1172] To a mixture of 5-(2-nitroethyl)-2-(pyrdin-3-yloxy)pyridine (157.0 mg, 0.64 mmol) described in Manufacturing Example 100-1-2 and methanol (6 mL) was added lithium methoxide (48.7 mg, 1,28 mmol), which was stirred for 1 hour at room temperature. The reaction solution was concentrated under a reduced pressure, which gave a white solid. To a mixture of a dichloromethane (4 mL) and tetrahydrofuran (2 mL) solution of this solid was added titanium tetrachloride (155.0 μL, 1.41 mmol) under nitrogen atmosphere at -78°C, which was stirred for another 3 hours at 0°C. Water was added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure. To a mixture of the residue thus obtained (30.7 mg), 3-ethynyl-pyridin-2ylamine (13.7 mg, 0.12 mmol) described in Manufacturing Example 1-2-3, tetrahydrofuran (1 mL), and dimethyl sulfoxide (1 mL) was added triethylamine (32.4 µL, 0.23 mmol) at room temperature, which was stirred for 1 hour at 55°C. The reaction mixture was cooled to room temperature, water was added thereto, which was then extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue thus obtained was purified by reverse-phase high performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trifluoroacetic acid), and then further purified by preparative thin-layer chromatography (NH silica gel, ethyl acetate) to obtain the title compound (1.41 mg, 4%).

1H-NMR Spectrum (CDCl₂) δ (ppm): 4.03 (2H, s), 5.39 (2H, brs), 6.28 (1H, s), 6.73 (1 H, ddd, J = 0.8, 4.8, 7.6 Hz), 6.98

(1 H, d, J = 8.4 Hz), 7.35 (1 H, dd, J = 4.8, 8.0 Hz), 7.51-7.54 (1 H, m), 7.67 (1 H, ddd, J = 0.2, 2.4, 8.4 Hz), 7.71 (1 H, dd, J = 2.0, 7.6 Hz), 8.11 (1 H, d, J = 2.8 Hz), 8.15-8.17 (1 H, m), 8.46 (1 H, d, J = 4.4 Hz), 8.50 (1 H, d, J = 2.4 Hz). The starting materials 51-2 nitrothiv)-2 (oviding -9 wook) volviding, was swithesized as follows.

5 [Manufacturing Example 100-1-1] 6-(Pyridin-3-yloxy)-pyridine-3-carbaldehyde

[1173]

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[1174] To a suspension of sodium hydride (407 mg, 8.48 mmol, 50% in oil) and N,N-dimethylformamide (45 mL) was added an N,N-dimethylformamide (5 mL) solution of 3-hydroxylyridine (806 mg, 8.48 mmol) at 70°C, which was stirred for 50 minutes. An N,N-dimethylformamide (5 mL) solution of 2-chloro-5-formyllyridine (1.0 g, 7.06 mmol) was added to this reaction mixture at the same temperature, which was estread of 5 hours at 100°C. The reaction mixture was cooled to room temperature, and water was added thereto, which was estracted with ethyl acetale. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filter of the compound (505.1 mg, 30°S).

1H-NMR Spectrum (DMSO-d_e) δ (ppm) : 7.32-7.36 (1 H, m), 7.53 (1 H, ddd, J = 0.8, 4.8, 8.4 Hz), 7.72-7.75 (1 H, m), 8.30-8.34 (1 H, m), 8.50-8.54 (2H, m), 8.70-8.72 (1 H, m), 10.01 (1 H, s).

[Manufacturing Example 100-1-2] 5-(2-Nitroethyl)-2-(pyridin-3-yloxy)pyridine

[1175]

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O'N O'N

[1176] A mixture of 6-(pyridin-3-yloxy)-pyridine-3-carbaldehyde (505.1 mg, 2.52 mmol) described in Manufacturing Exemple 100-1-1, nitromethane (800 pt., 12.5 mmol), ammonium acetate (886 mg, 5.04 mmol), and aceta exid (20 mt), was stirred for 2.5 hours at 14°C. This reaction mixture was cooled to mon temperature and partitioned in two water and ethyl acetate. The organic layer was separated, washed with water and saturated equeous sodium chloride, died over anhydrous magnesium suitate, and filtered. The filtrathe was concentrated under a reduced pressure. To a mixture of this residue in dimethyl suitoxide (20 mt), and acetic acid (2 mt), was added sodium borohydride (11-4.0 mg, 3.02 mmol) at room temperature, which was streed to 15 mixtures. Water was added to this reaction mixture, which was streed to 15 mixtures. Water was added to this reaction mixture, which was streed to 15 mixtures was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 2:1) to obtain the title compound (157.3 mg, 28%).

1+i-NMR Spectrum (DMSO-d_e) δ (ppm) : 3.23 (2H, t, J = 6.8 Hz), 4.88 (2H, t, J = 6.8 Hz), 7.18-7.22 (1 H, m), 7.77 (1 H, dd, J = 5.6, 8.4 Hz), 7.90 (1 H, dd, J = 2.4, 8.4 Hz), 8.02-8.07 (1 H, m), 8.07-8.10 (1 H, m), 8.45 (1 H, d, J = 6.0 Hz), 8.11 (1 H, d, J = 2.8 Hz).

[Example 101] 3-(3-(4-(5-Methyl-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1177]

[1178] The title compound (120 mg, 57%) was obtained according to the methods similar to those of Example 18, using 4-(5-(2,6-diamino-pyridin-3-yi)-isoxazo-1-yimethyl-jbrenol (150 mg, 0.53 mmol) described in Manufacturing Example 18-1-1 and 2-chiromethyl-5-methyl-pyridine (90 mg, 0.6 Hmol) described in Manufacturing Example 42-1-2. H+-NMR Spectrum (DMSO- d_0) δ (ppm): 2.29 (3H, s), 3.87 (2H, s), 5.10 (2H, s), 5.78 (2H, brs), 5.82 (1 H, d, J = 8.0 Hz), 7.50 (1 Hz), 8.00 (1 Hz), 9.50 (1 Hz), 9.

[Example 102] 3-(3-(4-(4-Methyl-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2, 6-diamine

20 [1179]

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2 [1180] To a terehydrodrunn (5.00 ml.) solution of (4-(4-methyl-pyridin-2-yloxymethyl)-phenyl)-acetorydroximoyl chio-ride (130 mg. 0.447 mmol) described in Manufacturing Example 43-1-5 and 3-ethynyl-pyridin-2-g-damine (30.0 mg. 0.226 mmol) described in Manufacturing Example 13-1-3 was added triethylamine (126 µL., 0.903 mmol) at room temperature, which was stried for 1 hour at room temperature. Water was added to the reaction solution at room tamperature, which was extracted with ethyl acetals. The organic layer was washed with saturated aqueous sodium chloride and offer offer or anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 2:1) to obtain the title compound (37.4 mg. 42.7%).

1H-NMR Spectrum (DMSO- d_0) δ (ppm) : 2.26 (3H, s), 3.95 (2H, s), 5.30 (2H, s), 5.79 (2H, brs), 5.83 (2H, d, J = 8.4 Hz), 6.11 (1H, brs), 6.37 (1H, s), 6.67-6.68 (1H, m), 6.81-6.83 (1H, m), 7.30 (2H, d, J = 8.0 Hz), 7.38 (2H, d, J = 8.0 Hz), 7.51 (1H, d, J = 8.4 Hz), 8.09-8.09 (1H, d, J = 5.2 Hz).

[Example 103] 3-(3-(4-(5-Methyl-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2, 6-diamine

[1181]

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[1182] To a tetrahydrotruran (5.00 mL) solution of (4.6-methyl-pytridin-2-ylocymethyl)-phenyl)-acatohydroximoyl chioride (130 mg, 0.447 mmol) described in Manufacturing Example 44-1.5 and 3-ethynyl-pytridin-2,6-diamine (30.0 mg, 0.226 mmol) described in Manufacturing Example 13-1-3 was added triethylamine (126 µL, 0.933 mmol) at room temperature, which was stirred for 2 hours at room temperature. Water was added to the reaction solution at room temperature, which was extracted with ethi valeata. The organic laver was washed with saturated solution shorties solution and dried over anlydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 2:1) to obtain the title compound (57.4 mg, 65.6%).
14 - NMR Spectrum (DMSO-dg.) & [ppm]: 2:20 (8H, s), 3:95 (2H, s), 5.28 (2H, s), 5.79 (2H, brs), 5.82 (1 H, d, J = 8.4 Hz), 6.11 (2H, brs), 6.36 (1 H, s), 6.76 (1 H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.38 (2H, d, J = 8.0 Hz), 7.59 (75 H, brs), 7.58 (75 H, b

[Example 104] 3-(3-(4-(6-Fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2, 6-diamine

[1183]

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[1184] To a tetrahytorfuran (3 mL) solution of 4-(5-(2, 6-diamino-pydiino-3-yh-isoxazol-3-yhmethyl-phenol (40 mg, 0.14 mmol) described in Manufacturing Example 18-11 was added a 51 sodium hydroxide aqueous solution (28 3 yl., 0.14 mmol) described with a final manufacturing Example 18-11 was added a 51 sodium hydroxide aqueous solution (28 x) yl., 0.14 mmol), which was discolved by irradiating ultrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white solid. To a suspension of this solid in N.N-dimethyformamide (1 mL) was added an N.N-dimethyformamide (2 mL) was partitioned into water and ethyria describe. The organic layer was separated, washed with water and seturated aqueous sodum chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by N thi slica gel column chromatography (using an acetonifrile-water mobile phase containing 0.1% to triflorosceptic sold esit. 1 whose in the title compound (7.8 mg.) 11 % os at filtritorosceptic sold esit.

1H- NMR Spectrum (CD₂OD) δ (ppm): 3.96 (2H, s), 5.08 (2H, s), 6.15 (1H, d, J = 8.8 Hz), 6.42 (1 H, s), 6.96 (2H, d, J = 8.8 Hz), 6.96-7.00 (1 H, m), 7.23 (2H, d, J = 8.4 Hz), 7.43-7.46 (1 H, m), 7.90 (1 H, d, J = 8.8 Hz), 7.94 (1 H, q, J = 8.4 7.6 Hz).

MS m/e (ESI) 391.99(MH+)

[Example 105] 3-(3-(4-(5-Methyl-furan-2-ylmethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1185]

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[1188] To a mixture of (4-(5-methyl-hura-2-ylmethyl)-penely)-acetohydroximoyl chloride (11 mg, 0.043 mmo) described in Manufacturing Example 46-1-6 and tetrahydrofurar (1 ml) were added 3-ethynyl-pyridrid-2-6 idamle (4.5 mg, 0.034 mmo) described in Manufacturing Example 13-1-3 and triethylamine (9.4 µL, 0.068 mmo), which was sitrred for 3 hours at 40°C. Water was added thereto at the same temperature, which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 3:2) to obtain the title compound (9.2 mr, 76%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 2.24 (3H, s), 3.89 (2H, s), 3.98 (2H, s), 4.53 (2H, br s), 5.31 (2H, br s), 5.84-5.87 (2H, m), 5.91 (1 H, d, J = 8.2 Hz), 5.99 (1 H, s), 7.20 (4H, d, J = 2.4 Hz), 7.48 (1 H, d, J = 8.2 Hz).

[Example 106] 3-(3-(5-p-Tolyloxy-thiophen-2-ylmethyl)-isoxazol-5-yl)-pyridin-2, 6-diamine

[1187]

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11188] To a tetrahydroturan (5.00 mL) solution of (5-p-tolytoxy-thiophen-2-yl-acetohydroximoy) chloride (130 mg. 0.461 mmol) described in Manufacturing Example 48-1-5 and 3-ethymly-pyrdin-2-6-diamine (30.0 mg. 0.226 mmol) obsorbed in Manufacturing Example 13-1-3 was added trethylemine (126 µL, 0.030 mmol), which was stirred for 7 hours at 60°C. Water was added to the reaction solution at room temperature, which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over enhydrous magnetium sulfate, and the solvent was everporated under a reduced pressure. The residue was purified by NNI silice gel column chrometography (zhi) acetate: betaten = 2:11 to obtain the title compound (12.0 mg. 1.40%).

1H-NMR Spectrum (CDCl₃) ô (ppm): 2.27 (3H, s), 4.08 (2H, s), 5.81 (2H, brs), 5.84 (1 H, d, J = 8.8 Hz), 6.13 (2H, brs), 6.44 (1 H, s), 6.47 (1 H, d, J = 3.6 Hz), 6.73 (1 H, d, J = 3.6 Hz), 6.98-7.01 (2H, m), 7.17-7.19 (2H, m), 7.54 (1 H, d, J = 8.8 Hz).

[Example 107] 3-(3-(4-(Pyridin-4-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2, 6-diamine

5 [1189]

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[1190] To a tetrahydrofuran (3 m.l.) solution of 4-(6-(2, 6-diamino-pyridin-3-yi)-isoxazol-3-yimethyl)-phenol (50 mg, 0.18 mmol) described in Manufacturing Exemple 18-1-1 was added a 6 N sodim hydroxide aqueous solution (56.4 µL) on 18 mmol), which was dissolved by irredating ultrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white solid. This solid was suspended in N, N-dimethylformamide (1 ml.). Meanwhile, THF (760 µL) and a 1 N sodium hydroxide aqueous solution (780 µL, 0.78 mmol) were added to 4-(chloromethylpyridine hydrochoide (100 mg, 0.78 mmol), and then the organic hydroxy was separated to obtain a tetrahydrofuna solution of 4-(chloromethylpyridine. A part of this solution (364 µL) was added to the above-mentioned N.N-dimethylformamide suspension and stirred for 14.5 hours at room temperature. This reaction mixture was partitioned into water and eithyl acettate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by MH allica del column chromostogrably (eithy acettate) to foliath the title compound (64.6 mg,

1H-MMR Spectrum (DMSO-d₀) δ (ppm): 3.88 (2H, s), 5.16 (2H, s), 5.79 (2H, brs), 5.82 (1 H, d, J = 8.4 Hz), 6.10 (2H, brs), 6.34 (1 H, s), 6.97 (2H, d, J = 8.4 Hz), 7.23 (2H, d, J = 8.8 Hz), 7.42 (2H, d, J = 5.2 Hz), 7.51 (1H, d, J = 8.4 Hz), 6.66 (2H, d, J = 5.2 Hz).

[Example 108] 3-(3-(4-(Pyridin-3-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2, 6-diamine

[1191]

[1192] To a tetrahydrofuvan (3 m.l.) solution of 4.(5 c.2,6 diamino pyridin 3-y)-isoazad/3 ylmentyly-prenol (60 mg.), 0.18 mmol) described in Manufacturing Example 18-1-1 was added a 5 N sodium hydroxide aqueous solution (35 d. µ.l., 0.18 mmol), which was dissolved by irradiating ultrasoric wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white solid. This solid was suspended in N, N-dimethylformatic (1 m.l.). Meanwhile, 1 http://dx.pu.n. part of a N is oddium Nyroxide aqueous solution (760 µ.l., 0.78 mmol) were added to 3-(chioromethylypyridine hydroxide aqueous solution (760 µ.l., 0.78 mmol) were added to 3-(chioromethylypyridine. Ap and for this solution (364 µ.l.) was added to the above-mentioned NN-dimethylformamide suspension and stirred for 15 hours at room temperature. This reaction mixture was pertitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over annydrous magnesium sulfate, and filtered. The filtrate was concentrated under an educed pressure. The residue was purified by NNI silica geli column chromatography (ethyl acetate) to obtain the title compound (4.9.6 mg, 75%). H-NMR Spectrum (DNSO-4g) 6 ppm; 3.88 (2), 8.5, 1.6 (24, h.), 5.7 (24), h.s., 5.7 (24), h.d., 5.8 (4), h.d., 5.7 (2), h.d., 5.8 (4), h.d., 5.7 (4), h.d., 5.8 (4), h.d., 5

[Example 109] 3-(3-(4-(4-Chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2, 6-diamine

[1193]

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[1194] To a tetrahydrofunan (3 mL) solution of 4-(5-(2, 6-diamino-pyridin-3-yh-)isoxazo/3-yhmethyl-phenol (30 mg, 0.11 mmol) described in Manufacturing Example 18-1-1 was added a 5 N sodium hydroxide aqueous solution (21.2 µ, 1, 0.11 mmol), which was dissolved by irradiating ultrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white solid. An N.N-dimethylformamid (1 mL) solution of 4-chioro-2-chioromethyl-pyridine (34.3 mg, 0.21 mmol) described in Manufacturing Example 51-1-2 was added to a suspension of his solid in N.N-dimethylformamide (1 mL), which was stirred for 1 hour at 80°C. This reaction mixture was cooled to room temperature and then partitioned into water and ethyl acetalst. The organic layer was separated, washed with water and saturated aqueous sodium chlorida, divid over anhydrous magnasium sulfate, and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by NH si licing est column chromatography (heatare: ethyl acetate = 1: 2), and then further purified by reverse-phase high performance liquid chromatography (using an acetonitrile-water mobile phase containing). 1% trifluoroacetic acid) to obtain the title compound (6.1 mg, 12%) as a triburo acetic acid stat. H-NAMR Spectrum (CL₂OO) 3 (ppm): 3.94 (21.4), 5.61 (24.4), 5.185 (11.4), 6.21 (11.4), 6.88 (21.4), 5.4 (21.4), 6.88 (21.4), 5.4 (21.4), 6.88 (21.4), 5.4 (21.4), 6.88 (21.4), 5.4 (21.4), 6.88 (21.4), 5.4 (21.4), 6.88 (21.4), 5.4 (21.4), 6.88 (21.4), 7.85-7.45 (11.4), 7.56 (11.4), 6.75 (11.4), 7.62-7.63 (11.4), 8.47 (11.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95 (21.4), 6.95

[Example 110] 3-(3-(4-(6-Chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1195]

[1196] To a tetrahydroutran (3 ml.) solution of 4-(5-(2,6-diamino-pyridin-3-yh-)isoxazo-3-syiieithyly-pneno (30 mg. 0.11 mmol), which was dissolved by irradiating lutrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white sollid An NI-A-dimethylformamide (1 ml.) solution of 2-chloro-6-chloromethyly-pyridine (34.3 mg. 0.21 mmol) described in Manufacturing Example 52-1-2 was added to a suspension of this sollid in NI-A-dimethylformamide (1 ml.), which was stirred for 1 hour at 60°C. This reaction mixture was cooled to room temperature and then partitioned into water and ethyl acettate. The organic luyer was separated, washed with water and saturated aqueous sodium childride, died over anhydrous magnesium sultate, and filtered. The filtrate was concentrated under a reduced pressure. The residue was printed by NH silica gel column chromatography (heptane : ethyl acettae = 1:2), and then further purified by reverse-phase high performance liquid chromatography (using an acetontirile-water mobile phase containing 0.1 % triflicrocacetic acid) to othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the title compound (1.5 mg. 37%) as a triflicrocacetic acid; bot othis the titl

[Example 111] 3-(3-(6-Phenoxymethyl-pyridin-3-vimethyl)-isoxazol-5-vl)-pyridin-2.6-diamine

[1197]

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[1188] To a tetrahydroturan (5.00 mL) solution of (6-phenoxymethy4-pyridin-3-y4)-acatohydroximoyl cholnde (88.0 mg, 0.382 mmol) described in Manufacturing Example 54-16-8 and 3-ethynyt-pyridin-2-6-diamine (25.0 mg, 0.188 mmol) described in Manufacturing Example 13-1-3 was added triethylamine (78.6 μL, 0.564 mmol) at room temperature, which was sitred for 4.5 hours at room temperature. Water was added to the reaction solution at room temperature, which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:1 → 3:1) to obtain the title compound (21.0 mg, 9.9%).

1H-NMR Spectrum (DMSO-d_b) δ (ppm): 4.02 (2H, s), 5.15 (2H, s), 5.81 (2H, brs), 5.83 (1 H, d, J = 8.4 Hz), 6.12 (2H, brs), 6.43 (1 H, s), 6.92-6.96 (1 H, m), 7.01 (2H, d, J = 8.4 Hz), 7.27-7.31 (2H, m), 7.50 (2H, dd, J = 4.0, 16.4 Hz), 7.47-7.71 (H, m), 8.56 (1 H, d, J = 2.4 Hz).

[Example 112] 3-(3-(4-(5-Fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1199]

1200] To a tetralydroturan (3 mL) solution of 4-(5-(2-6-diamino-pyridin-3-yl)-souzac)-3-ymethyl-phenoi (25.5 mg. 0.09 mmol) described in Manufacturing Example 16-11-was added a 5 N sodium hydroxide aqueous soultion (18.1 mg. 0.09 mmol), which was dissolved by Irradiating ultrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white solid. An NN-dimethylomamide (1 mL) solid or 2-chioromethyl-5-fluoro-pyriding (13.2 mg. 0.09 mmol) described in manufacturing Example 411-12- was added to a claspersion of this fluoro-pyriding (13.2 mg. 0.09 mmol) described in manufacturing Example 411-12- was added to a claspersion of this temperature and then partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered. The fiftrate was concentrated under a reduced pressure. The residue was purified by reverse-phase high performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (23.5 mg. 47%) as a diffiltomacetic acid sid.

¹H-NMR Spectrum (DMSO-D₆) 8 (ppm): 3.93 (2H, s), 5.15 (2H, s), 6.04 (1 H, d, J = 8.4 Hz), 8.53 (1 H, s), 6.98 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.577.61 (1 H, m), 7.77 (1 H, dt, J = 2.8, 8.8 Hz), 7.81-7.86 (1 H, m), 8.57 (1 H, d), J = 2.8 Hz).

MS m/e (ESI) 391.96(MH+)

Example 113] 3-(3-(4-(6-Fluoro-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1201]

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[1202] To a tetrahydrofuran (3 m.L) solution of (4-(6-fluoro-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride (200 mg. 0.678 mmol) described in Manufacturing Example 18-1-3 end 3-ethyl-ypyridin-2-yloxymethyl-phenyl-2-g-diamine (57.6 mg. 0.433 mmol) described in Manufacturing Example 13-1-3 was added triethylamine (236 k.L.1 mmol). This mixture was stirred for 2 hours at room temperature. This mixture was partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium suifate, and filtered. The filtrahe was concentrated under a reduced pressure. The residue was purified by NH silica egel column chromatography (neptane: ethyl acetate = 1: 1 - ethyl acetate) to obtain the title compound (150 mg. 57%).

1H-NMR Spectrum (CDCl₃ 6 (ppm): 4.02 (2H, s), 4.57 (2H, brs), 5.32 (2H, s), 5.34(2H, brs), 5.91-5.93 (1 H, m), 6.00 (1 H, s)), 6.47-6.50 (1 H, m), 6.64-6.66 (1 H, m), 7.30 (2H, d, J = 8.0 Hz), 7.42 (2H, d, J = 8.0 Hz), 7.48-7.50(1 H, m), 7.82-7.68(1 H, m).

[Example 114] 3-(3-(4-(5-Fluoro-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1203]

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[1204] To a tetrahydroturan (3 mL) solution of (4-(5-fluor-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride (200 mg. 0.679 mmol) described in Manufacturing Example 58-1-5 and 3-ethynyl-pridin-2-disamine (6.77 mg. 0.433 mmol) described in Manufacturing Example 13-1-3 was added triethylamine (237 mL. 1.7 mmol). The mixture was stirred for 4 hours at room temperature. This mixture was partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over antrydrous magnesium suifitae, and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by NH silica get column chromatography (heptane: ethyl acetate) = 1.7 ethyl acetate) to obtain the title compound (86 mg. 32%).

1H.NMR Spectrum (CDCl₃) δ (ppm): 4.03 (2H, s), 4.62 (2H, brs), 5.07(2H, s), 5.39 (2H, brs), 5.92-5.94(1 H, m), 6.00 (1 H, s), 7.13-7.16 (1 H, m), 7.31-7.33 (2H, m), 7.35-7.38 (3H, m), 7.49-7.51 (1H, m), 8.11-8.12(1H, m),

[Example 115] 3-(3-(1-Benzyl-1 H-pyrrol-3-vimethyl)-isoxazol-5-vi)- pyridin-2.6-diamine

[1205]

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[1206] The title compound (7.6 mg, 2.0%) was obtained according to the method similar to those of Example 3, using (1-benzyl-1-H-pyrrol-3-yl)acetohydroximoyl chloride (280 mg, 1.1 mmol) described in Manufacturing Example 57-1-3 and 3-ethynyl-pyridin-2,6-diamine (74 mg, 0.56 mmol) described in Manufacturing Example 13-1-3.

14-NMR Spectrum (DMSO-d₃) & (ppm): 3.70 (2H, s), 5.02 (2H, s), 5.77 (2H, brs), 5.83 (1 H, d, J = 8.0 Hz), 5.97 (1 H, dd, J = 2.0, 2.0 Hz), 6.09 (2H, brs), 6.35 (1 H, s), 6.70 (1 H, dd, J = 2.0, 2.0 Hz), 6.74 (1 H, dd, J = 2.0, 2.0 Hz), 7.18 (2H, d, J = 7.6 Hz), 7.29-7.29 (1 H, m), 7.30-7.35 (2H, m), 7.51 (1 H, d, J = 8.0 Hz).

[Example 116] 3-(3-(6-(4-Fluoro-benzyloxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1207]

[1208] To a tetrahydrofuran (10.0 mL) solution of (6: (4-fluoro-benzyloxy)-pyridin-3-yl)-acetohydroximoyl-chloride (133 mg, 0.450 mmol) described in Manufacturing Example 58-1-3 and 3-ethynyi-pyridin-2,6-diamine (30.0 mg, 0.225 mmol) described in Manufacturing Example 13-1-3 was added triethylamine (49.1 LL). 0.675 mmol), which was sirred for 3 hours at room temperature. Water was added to the reaction solution at room temperature, which was extracted with ethyl acetale. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulflate, and the solvent was evaporated under a reduced pressure. The residue was purified by VH Billica cale

column chromatography (ethyl acetate : heptane = 3 : 1) to obtain the title compound (67.4 mg, 76.5%).

1H-NMR Spectrum (DMSO-d₂) & (ppm) : 3.82 (2H, s), 5.31 (2H, s), 5.81 (2H, brs), 5.83 (1 H, d, J = 8.4 Hz), 6.12 (2H, brs), 6.40 (1 H, s), 6.84 (1 H, d, 8.4 Hz), 7.19 (2H, d, J = 8.8 Hz), 7.47-7.53 (3H, m), 7.65-7.67 (1H, m), 8.14 (1H, d, J = 2.0 Hz).

[Example 117] 3-(3-(4-(4-Fluoro-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1209]

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HAT NHA

20 [120] To a tetrahydrofuran (3 mL), solution of (4-(4-fluor-pyridin-2-ylovymethyl)-phenyl)-acotohydroximoyl chloride (200 mg, 0.678 mmol) described in Maunfacturing Example 61-5 and 3-ethynyl-pyridin-2-fludienine (57.7 mg, 0.483 mmol) described in Manufacturing Example 13-13 was added triethylamine (237 mL, 1.7 mmol). This mixture was stirred for 4 hours at room temperature. This incluture was partitioned into water and ethyl acetaet. The organic layer was separated, washed with water and saturated aqueous sodium chloride, diede over enhydrous megnesium sulfate, and 55 filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column cirromatoropathy (heatina; e. Fully acetate) 1 = 1 - ethyl acetaet 1 = 1 - ethyl acetaet 1 = 1 - ethyl acetaet 1 = 1.

¹H-NMR Spectrum (CD₃OD) δ (ppm): 4.02 (2H, s), 5.18 (2H, s), 5.94-5.96 (1H, m), 6.23 (1 H, s), 6.99-7.01 (1 H, m), 7.097-7.103 (1 H, m), 7.34-7.36 (2H, m), 7.40-7.42 (2H, m), 7.54-7.56 (1H, m), 8.14-8.15 (1H, m).

[Example 118] 3-(3-(3-(Pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1211]

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H N N NH.

11212 To a tetrallydrofuran (3 m.l.) solution of 3-(pyridin-2-yinethoxy)-phenyl-acetohydroximoy) chloride (200 mg. 07.23 mmol) described in Manufacturing Example 60-1-4 and 3-ethymyl-pyridin-2,6-dismine (61.4 mg. 0.461 mmol) described in Manufacturing Example 13-1-3 was added trietlylarine (252 µl., 1.81 mmol). This mixture was stirred for 2 hours at room temperature. This mixture was partitioned into water and ethyl acetale. The original layer was separatriced, wasted with water and saturated aqueous sodium chloride, dired over analydrous magnetism suffatel, and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl scetales: 11: 1- 4 mly scetales 10: 10-4 mly scetales

H-INMR Spectrum (CD₃OD 8 (ppm): 3.96 (2H, s), 5.16 (2H, s), 5.94-5.97 (1H, m), 6.17 (1 H, s), 6.87-6.92 (3H, m), 7.21-7.25 (1 H, m), 7.29-7.32 (1 H, m), 7.53-7.57 (2H, m), 7.79-7.84 (1 H, m), 8.48-8.50 (1H, m),

[Example 119] 3-(3-(3-Benzyloxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

55 [1213]

[1214] To a tetrahydrofusar (S ml.) solution of (3-benz/foxy-phenyl)-acetohydroxarroy/chloride (200 mg, 0.724 mmo) described in Manufacturing Example 61-14 and 5-thymyl-pytidin-2,6-defamine (615 mg, 0.482 mmo) described in Manufacturing Example 13-1-3 was added triethyfamine (252 μL, 1.81 mmo). This mixture was stirred for 4 hours at room temperature. This mixture was partitioned into water and ethyl acetale. The organic layer was sepretad, washed with water and exturated aqueous osdium chloride, rided over antyferious magnesium suite, and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by NH-silica gelcolumn chromatography(heptane : ethyl acetate 1:1-i erhyl acetate 1:1-i erhyl acetate 1:1-i erhyl acetate 3:1-i erhyl acetate 3:1-i

¹H-NMR Spectrum (CD₃OD) δ (ppm): 3.95 (2H, s), 5.07 (2H, s), 5.95-5.97 (1H, m), 6.17 (1 H, s), 6.86-6.88 (2H, m), 6.92 (1 H, m), 7.20-7.27 (2H, m), 7.31-7.35 (2H, m), 7.39-7.41 (2H, m), 7.53-7.55 (1 H, m).

[Example 120] 3-(3-(4-(5-Chloro-furan-2-vlmethyl)-benzyl)-isoxazol-5-vl)-pyridin-2,6-diamine

[1215]

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[1216] To a mixture of (4-(5-chloro-furan-2-yimethyl)-phenyl)-acetohydroximoyl chloride (25 mg, 0.088 mmol) described in Manufacturing Example 82-1-6 and tetrahydrofuran (1 mL) were added 3-ethynyl-pyridin-2-6-diamine (9 mg, 0.088 mmol) described in Manufacturing Example 13-1-3 and triethylmine (19 mL, 0.1 fmmol), which was sirred for 1 hour at room temperature. Water was added to the reaction mixture at the same temperature, which was extracted with early acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by reverse-phase high performance liquid chromatography (using an acetonitrie-water mobile phase containing 0.1 % trifluoroscetic acid) to obtain the title compound as a trifluoroscetate (10 mg, 28%).

MS m/e(ESI) 381.13(MH+)

[Example 121] 3-(3-(5-Phenoxy-pyridin-2-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1217]

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[1218] The title compound (26 mg, 34%) was obtained according to the method similar to those of Example 3, using (5-phenoxy-pyridin-2yl)-acetohydroximoyl chloride (56 mg, 0.21 mmol) described in Manufacturing Example 121-1-5 and 3-ethynyl-pyridin-2,6-diamine (42 mg, 0.32 mmol) described in Manufacturing Example 13-1-3.

¹H-NMR Spectrum (DMSO-d_e) δ (ppm): 4.11 (2H, s), 5.80 (2H, brs), 5.83 (1 H, d, J = 8.0 Hz), 6.12 (2H, brs), 6.40 (1 H, s), 7.05 (2H, d, J = 8.0 Hz), 8.31 (1 H, s), 7.51 (2H, m), 7.38-7.45 (4H, m), 7.25 (1 H, d, J = 8.0 Hz), 8.31 (1 H, s), 17.12191 The starting material. (5-ohenoxy-origin-2-VI) actohydroximovl chloride, was syrthesized as follows:

5 [Manufacturing Example 121-1-1] 2-Methyl-5-phenoxy-pyridine

[1220]

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[1221] Diphenyliodonium iodide (5.8 g. 14 mmol), 3-hydroxy-6-methylpyridine (1.8 g. 14 mmol), potassium tert-butoxide (1.7 g. 15 mmol), and tertahydroturan (60 mL) were stirred for 2.5 hours at 60°C. Water was added to the reaction solution, which was extracted with tryl acateta. The solvent was exproaded under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acateta te = 3:1) to obtain the title compound (1.5 g. 56%). 1H-NMR Spectrum (DMSO-dg) 6 (ppm): 2.46 (3H, s), 7.00-7.04 (2H, m.), 7.13-7.18 (1 H, m), 7.28 (1 H, d, J = 8.4 Hz), 7.377, 43 (2 H, m, 8.24 (1 H, d, J = 2.4 Hz).

[Manufacturing Example 121-1-2] (5-Phenoxy-pyridin-2-yi)-methanol

25 [1222]

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HO ()

[1223] A mixture of 2-methyl-5-phenoxy-pyridine (3.6 g. 19 mmol) described in Manufacturing Example 121-1-1, 3-chioroperoxybezolocald (5.6 g. 33 mmol), and methylene cholinde (80 mL) was stirred at room temperature for 45 minutes. Aqueous sodium sulfite was added to the reaction solution, and the organic layer was separated and was washed with 5 N aqueous sodium hydroxide (7 mL). The organic layer was dried over anhydrous magnesium sulfate, and then the solvent was evaporated under a reduced pressure to obtain 2-methyl-5-phenoxy-pyridine 1-oxide (3.3 g). 2-methyl-5-phenoxy-pyridine 1-oxide (3.3 g), 2-methyl-5-phenoxy-pyridine 1-oxide (3.3 g), 2-methyl-5-phenoxy-pyridine 1-oxide (3.3 g). 2-methyl-5-phenoxy-pyridine 1-oxide (3.3 g), 2-methyl-5-phenoxy-pyridine 1-oxide (3.3 g), 2-methyl-5-phenoxy-pyridine was exporated under a reduced pressure, and the origanic layer was separated. The ethyl sociate solution was concentrated under a reduced pressure, and the redictive was purified by sillice age clotulum-chromotography (hepticae: citryl acetate = 2 1; to oxide an acetic acid 5-phenoxy-pyridin-2-yimethyl ester (3.0 g, 12 mmol), 5 N aqueous sodium hydroxide (3.0 mL), and methanol (2.0 mL) were stirred for 20 minutes at 60°C. Water and ethyl acetate were added to the reaction solution, and the origanic layer was separated. The ethyl sociate layer was dried over anthyrdrous magnesium sulfate, and then the solvent was evaporated under a reduced pressure to oxide the title compound (2.6 g, 65%).

(1 H, m), 7.38-7.53 (4H, m), 8.29 (1 H, d, J = 2.8 Hz).

[Manufacturing Example 121-1-3] 5-Phenoxy-pyridine-2-carbaldehyde

[1224]

[1225] (5-Phenoxy-pyridin-2-yl)-methanol (300 mg, 1.5 mmol) described in Manufacturing Example 121-1-2, magnesium(IV) oxide (1.3 g, 15 mmol), and acetone (10 mL) were stirred under reflux for 20 minutex. More magnesium (IV) oxide (1.5 g, 17 mmol) was then added, which was stirred under reflux for another 20 minutex. The reaction solution was filtered through a Cellie pad, and then the filtrate was concentrated under a reduced pressure to obtain the title compound (220 mm, 73%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 7.20-7.25 (2H, m), 7.29-7.34 (1 H, m), 7.47-7.54 (3H, m), 7.95-8.00 (1 H, m), 8.57-8.60 (1 H, m), 9.94 (1 H, s).

[Manufacturing Example 121-1-4] 2-(2-Nitro-ethyl)-5-phenoxy-pyridine

[1226]

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[1227] A mixture of 5-phenory-pyridine-2-archalatelyte (700 mg, 3.5 mmnb) described in Manufacturing Example 21-1-3, lithius methodale (170 mg, 4.6 mmnb), indirentatine (280 mg, 4.6 mmol), and methodale (170 mg, 4.6 mmol), and which was effored for 10 minutes at room temperature, after which the reaction solution was concentrated under a reduced pressure. Eithyl acetate was added to the residue, and the organic layer was separated and wished with saturated aqueous sodium-chloride once and then ded over enhydrous magnesium sulfate. The solvent was exported under a reduced pressure, dimetryl sulfoxied (50 mL), acetale acid (0.50 mL), and sodium borohydride (270 mg, 7.0 mmol) were added to the residue, which was stared for 5 minutes at room temperature. Water and eithyl acetate were added to the reaction solution, and then the ethyl acetate layer was separated and washed with aqueous sodium bicarbonate, water, and saturated aqueous sodium bicarbonate, solvent was evoporated under a reduced pressure, and the residue was purified first by silicia gel column chromatography (heptane : ethyl acetate = 2: 1) and then NH silicia gel column chromatography (heptane : ethyl acetate = 2: 1) and then NH silicia gel column chromatography (heptane : ethyl acetate = 4: 11 her in the compound (76 mg, 8.9%).

¹H-NMR Spectrum (DMSO- d_6) δ (ppm) : 3.40 (2H,d, J = 6.4 Hz), 4.98 (2H, d, J = 6.4 Hz), 7.02-7.06 (2H, m), 7.16-7.21 (1 H, m), 7.39-7,46 (4H, m), 8.28 (1 H, d, J = 2.4 Hz).

[Manufacturing Example 121-1-5] (5-Phenoxy-pyridin-2-yl)-acetohydroximoyl chloride

^{[5} [1228]

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[1229] To 2-(2-nitro-ethyl)-5-phenoxy-pyridine (76 mg, 0.31 mmol) described in Manufacturing Example 121-1-1 and methanol (6.0 ml.) was added lithium methoxide (24 mg, 0.62 mmol) at room temperature, which was stirred for 3 mitrutes, and then the solvent was everporated under a reduced pressure. Methylene chloride (10 ml.) was added to the residue, titanium(IV) chloride (0.11 ml., 1.0 mmol) was added at room temperature, which was stirred for 10 minutes. Cold aqueous sodium bicarbonate and ethyl acetate were added to the reaction solution, which was filtered through a Cellie pad, and then the organic lever was separated. The organic lever was concentrated under a reduced pressure

to obtain the title compound (56 mg, 69%).

 1 H-NMR Spectrum (DMSO-d₀) δ (ppm) : 3.99 (2H, s), 7.00-7.10 (2H, m), 7.13-7.22 (1 H, m), 7.34-7.48 (4H, m), 8.32 (1 H, d, J = 2.4 Hz), 11.75 (1 H, s).

5 [Example 122] 3-(3-(4-(5-Chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1230]

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N, NH₂

[1231] To a letrahydrofuran (3 m.l.) solution of 4-(5-(2,6-diamino-pyridin-3-y)-isoxazol-3-ymethyl)-phenol (30 m.g. 0.11 mmol) desoribed in Manufacturing Example 18-1-1 was added a 5 N sodium hydroxide aqueous solution (21,2 µ., 0.11 mmol), which was dissolved by irradiating ultrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white solid. An N,N-dimethylformamide (1 m.l.) solution of 5-chloro-2-chioromethylydridine (18 at m.g. 0.12 mmol) desorbed in manufacturing Example 36-1-2 was added to a suspension of this solid in N,N-dimethylformamide (1 m.l.), which was stiffred for 1 hour at 60°C. The reaction mixture was cooled to room temperature and then partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dired over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heplane: ethyl acetate = 1: 1) to obtain the title compound (34 m.g. 89%).

1H-NMR Spectrum (DMSO-d₀) 8 (ppm): 3.88 (2H, s), 5.16 (2H, s), 5.79 (2H, brs), 5.82 (1 H, d, J = 8.4 Hz), 6.11 (2H, brs), 6.34 (1 H, g, 6.97 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 8.8 Hz), 7.51 (1 H, d, J = 8.4 Hz), 7.54 (1 H, d, J = 8.4 Hz), 7.96 (1 H, dd, J = 2.4 Hz), 8.31 (1 H, d, J = 2.8 Hz).

[Example 123] 3-(3-(3-Phenoxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1232]

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H,N N NH,

[1233] To a teixahydrofuran (10.0 mL) solution of (3-phenoxy-phenyt)-acotohydroximoyl chloride (133 m.g. 0.508 mmo) described in Manufacturing Example 64-1-3 and 3-ethynyl-pyridine-2,6-diamine (30.0 m.g. 0.254 mmol) atroom temperature, which was stirred for 14 hours at room temperature. Water was added to the reaction solution at room temperature, which was stirred with eithy accetate. The organic layer was vashed with eathyrated aqueous sodium chloride and risid over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl accetate heptane = 3: 1) to obtain the title compound (26.1 mg, 30.6%).

11-NMR Spectrum (CD,QD) & polymin 3.39 (214 h.g.) & 3.81 (214, b.g. 12, 24 H.g., 6.12 (24.1 H.g., 6.12 (24.1 p.s.), 6.36 (1 H., b.g.), 6.36 (1 H.,

s), 6.84-6.87 (1 H, m), 6.98-7.02 (3H, m), 7.07 (1H, d, J = 8.0 Hz), 7.12-7.16 (1 H, m), 7.31-7.41 (3H, m), 7.52(1 H, d, J = 8.4 Hz).

[Example 124] 3-(3-(3-Butoxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1234]

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H₃N NH₃

[1235] To a tetrahydroturan (3 m.l.) solution of (3-butoxy-phenyl)-acetohydroximoyl chloride (150 mg, 0.621 mmo)) described in Manufacturing Exemple 65-1-4 and 3-ethymyl-pyrith-2,6-diamine (52.8 mg, 0.398 mmo) described in Manufacturing Exemple 13-1-3 was added trierhylamine (2-16 µL, 1.55 mmo). This mixture was sittred of hours at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water and saturated aqueous sodium chloride, vided over anlydrows magnesium surface, and filterof. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate; 6 herbare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to obtain the title commount (43 mg, 21 Febrare = 1:1 1 - ethyl acetate) to

¹H-NMR Spectrum (CDCl₃) δ (ppm): 0.95-0.98 (3H, m), 1.45-1.51 (2H, m), 1.72-1.77 (2H, m), 3.96-3.99 (2H, m), 3.98 (2H, s), 4.59 (2H, brs), 5.36 (2H, brs), 5.91-5.93 (1 H, m), 6.01 (1 H, s), 6.78-6.86 (4H, m), 7,21-7.24 (1 H, m).

[Example 125] 3-(3-(3-Cyclopropylmethoxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1236]

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H.N. N. NH.

[1237] To a tetrahydrofuran (3 m.), solution of (3-cyclopropylmethoxy-phenyl)-acetohydroximoyl chloride (150 mg, 0.826 mmol) described in Manufacturing Example 61-4 and 3-ethyl-pyrdint-2.6-diamine (53.2 mg, 0.399 mmol) described in Manufacturing Example 13-1-3 was added interhylamine (216 µL, 157 mmol). This mixture was stirred for 40 hours at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water and saturated equeous sodium chloride, dried over enhydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1.1 - ethyl acetate) to obtain the title compound (117 mg, 65%).

¹H-NMR Spectrum (CDCl₂) δ (ppm): 0.32-0.36 (2H, m), 0.61-0.66 (2H, m), 1.22-1.29 (1H, m), 3.77-3.79 (2H, m), 3.86 (2H, s), 4.56 (2H, brs), 5.35 (2H, brs), 5.91-5.93 (1 H, m), 6.00 (1 H, s), 6.78-6.87 (3H, m), 7.21-7.25 (1 H, m), 7.48-7.50 (1H, m).

[Example 126] 3-(3-(4-Butoxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

0 [1238]

[1238] To a sterahydrofuran (3 ml.) solution of (4 butony phenryl)-seatohydroximoyl chloride (150 mg. 0.821 mmo)) described in Manufacturing Example (37-14 and 3-ethynyl-pyridin-2,6-diamine (62.8 mg. 0.398 mmol) described in Manufacturing Example (31-13 was added triethyramine (216 µL, 1.55 mmol). This mixture was stirred for 4 hours at room temperature. The mixture was partitioned into ethyl scettle and water. The organic layer was separated, washed with water and saturated aqueues sodium chloride, ordict over anythrous magnesium sutate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl scettes it or heptace at 1: 1-4 mly actestle) to other sidule was purified by NH silica gel column chromatography (ethyl scettes it or heptace at 1: 1-4 mly actestle) to other sidule was purified by NH silica gel column chromatography (ethyl scettes) to shall the title compound (155 mg. 74 hours).

¹H-NMR Spectrum (CDCl₃) 6 (ppm): 0.95-0.99 (3H, m), 1.46-1.53 (2H, m), 1.72-1.79 (2H, m), 3.92-3.96 (4H, m), 4.60 (2H, brs), 5.37 (2H, brs), 5.91-5.92 (1 H, m), 5.98(1 H, s), 6.84-6.86 (2H, m), 7.17-7.19 (2H, m), 7.48-7.50(1 H, m).

[Example 127] 3-(3-(5-Benzyloxy-pyridin-2-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1240]

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[1241] To a mixture of 2-(5-benzytoxy-yn/din-2-yl)-N-hydroxy-acetamidine (60 mg, 0.19 mmol) described in Manufacturing Example 127-15 and a 5 hydrochoric acid aqueous solution (1 mL) was added sodium initite (20 mg, 0.28 mmol) at 0°C, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium hohorids, dired over anhylorous magnesium suitlets, and filtered. The fittante was concentrated under a reclused pressure. To a tetrahydrofuran (3 mL) solution of this residue were added 3-ethynyl-pyridin-2-6-diamine (10 mg, 0.38 mmol) described in Marufacturing Example 13-13 and triethyntering (27 ML, 0.19 mmol), which was strended roth minutes at 50°C under nitrogen atmosphere. Water was added to the reaction mixture at room temperatura, which was addred with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dired over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (einly acetate: heptane = 2: 1), and then purified further by reverse-phase high performance liglical chromatography (lusing an accidentified-water mobile phase containing 0.1 % influoroacetic acid) to obtain the title compound (4.7 mg, 4.0%) as a difirilluoroacetic acid salt.

[1242] The starting material, 2-(5-benzyloxy-pyridin-2-yl)-N-hydroxy-acetamidine, was synthesized as follows.

[Manufacturing Example 127-1-1] 5-Benzyloxy-2-methyl-pyridine

[1243]

[1244] To an N.N-dimentylformamide (50 mL) solution of 3-hydroxy-6-methyltyridine (5.00 g. 48.8 mmol) was added sodium hydride (2.02 g. 50.4 mmol) (80% in oil), which was stirred for 16 minutes at 0°C. Next, heavyl formide (6.99 mL, 50.4 mmol) was added to this reaction mixture at 0°C, which was stirred for 3.5 hours at nom temperature. Water was added to the reaction mixture, which was extracted with ethyl acotate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl scatter e.2.11) to obtain the title compound (5.99 a. 68%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.49 (3H, s), 5.08 (2H, s), 7.05 (1 H, d, J = 8.6 Hz), 7.17 (1 H, dd, J = 2.9, 8.4 Hz), 7.31-7.44 (5H, m), 8.27 (1 H, d, J = 2.9 Hz).

[Manufacturing Example 127-1-2] (5-Benzyloxy-pyridin-2-yl)-methanol

20 [1245]

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[1246] To a methylene chloride (100 mL) solution of 5-benzyloxy-2-methyl-pyridine (5.99 g, 30.1 mmol) described in Manufacturing Example 127-1-1 was added m-chloroperbenzio's acid (8.79 g, 33.1 mmon), purity, 65%) at 0°C, which was stirred for 2-bours at room temperature. Saturated aqueous sodium bicarbonate was added to the reaction inhibitor at 0°C, which was extracted with methylene chloride. The organic layer was separated, washed with saturated aqueous sodium chloride, defed over analytorus magnesium sultate, and filtered. The filtrate was concentrated under a reduced pressur to obtain 5-benzyloxy-2-methyl-pyridine-1-oxide (7.71 g). Accide inhydride (7m Ju) was added to 5-benzyloxy-2-methyl-pyridine-1-oxide (7.71 g). Accide charged the construction of the residue was added a 5 N sodium hydroxide aqueous solution (7 mL), which was stried for 50 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. To an ethanol (50 mL) solution of this residue was added a 5 N sodium hydroxide aqueous solution (7 mL), which was stried for 50 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. The residue was partitioned into saturated aqueous sodium chloride, did over antrydrox magnesium sultate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane : ethy accide = 1: 1) to obtain the title compound (4.17 g, 54%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 4.46 (2H, d, J = 5.9 Hz), 5.15 (2H, s), 5.26 (1 H, t, J = 5.9 Hz), 7.29-7.40 (4H, m), 7.42-7.45 (3H, m), 8.22 (1 H, d, J = 2.9 Hz).

[Manufacturing Example 127-1-3] 5-Benzyloxy-2-chloromethyl-pyridine

0 [1247]

[1248] To a carbon tetrachloride (10 mL) solution of (5-benz)(oxy-pyrdidin-2-yy)-methanol (500 mg) described in Manindecturing Example 127-1-2 was added triphenylphosphire (791 mg), which was refluxed for 19 hours and 35 minutes under nitrogen atmosphere. The reaction mixture was cooled to room temperature and then concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 3:1) to obtain the fillic arcmonut/ (386 mc).

¹H-NMR Spectrum (CDCl₃) δ (ppm):4.64 (2H, s), 5.12 (2H, s), 7.25-7.28 (1H, m), 7.35-7.44 (6H, m), 8.34 (1 H, d, J = 2.7 Hz).

[Manufacturing Example 127-1-4] (5-Benzyloxy-pyridin-2-yl)-acetonitrile

[1249]

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[1250] To a solution of 5-benzyloxy-2-chloromethyl-pyridine (2.15 g, 9.11 mmoh) described in Menufacturing Example 127-13 in ethanol (30 mL) and water (10 mL) was added sodium cyanide (580 mg, 11.8 mmoh), which was stirred for 4 hours and 25 minutes under reflux. Water was added to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous magnesium suffate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate 1: 1) to bottain the title compound (1.77 q, 87%).

¹H-NMR Spectrum (CDCl₃) δ (ppm):3.88 (2H, s), 5.12 (2H, s), 7.29 (1H, d, J = 2.7 Hz), 7.32-7.42 (6H, m), 8.33 (1 H, d, J = 2.7 Hz).

[Manufacturing Example 127-1-5] 2-(5-Benzyloxy-pyridin-2-yl)-N-hydroxyacetamidine

[1251]

[1252] To an ethanol (30 mL) solution of (5-benzyloxy-pyridin-2-yl-)-acotonitrile (1.77 g. 7.89 mmol) described in Maninacturing Example 127-14 were added hydroxylammonium chloride (848 mg. 1.18 mmol) and potassium carbonate (2.18 g. 15.8 mmol), which was etimed for 11 hours and 20 minutes at 70°C. The mixture was then stirred for another 5 hours and 45 minutes under reflux. Water was added to the reaction mixture at room temperature, which was sotracted with ethyla cestea. The organic layer was separated, dried over anyhydrous magnesism sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate): methanol = 10:11) to obtain the title compound (560 mg. 27%).

 1 H-NMR Spectrum (DMSO-d₀) δ (ppm):3.61 (2H, s), 5.15 (2H, s), 7.21 (1H, d, J = 8.4 Hz), 7.32-7.47 (6H, m), 8.08 (1 H, s), 8.22 (1 H, d, J = 3.1 Hz), 8.32 (1 H, s), 9.49 (1H, s).

[Example 128] 3-(3-(4-Benzylamino-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1253]

126 [1254] To a tetrahydrofuran (3 m.), solution of (4-benzylamino-phenyl)-acetohydroxinmoy chlorida (150 mg, 0.546 mmol) described in Manufacturing Example 68-1-4 and 3-ethynyl-pyridin-2,6-diamine (48.4 mg, 0.348 mmol) described in Manufacturing Example 13-1-3 was added triethylamine (190 µL, 1.37 mmol). The mixture was stirred for 6.5 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water and saturated aqueous sodium chilorida, diried over anhydrous magnissism usitate, and filtered. The filtrate of the contraction of the contraction of the contracted under a reduced pressure, and the residue was purified by NH silica gel column chromatography (hostina: ethyl acetate = 11. ethyl acetate) to obtain the title compound (17 m, 8.4%).

¹H - NMR Spectrum (CDCl₃) δ (ppm): 3.89 (2H, s), 4.31 (2H, s), 4.52-4.58 (2H, m), 5.33 (2H, brs), 5.90-5.92 (1 H, m), 5.99 (1 H, s), 6.58-6.62 (2H, m), 7.07-7.09 (2H, m), 7.25-7.38 (5H, m), 7.48-7.52 (1 H, m).

[1255] Note that it was not observed that proton on the amino group of NH-CH2Ph appeared on the NMR chart.

[Example 129] 3-(3-(4-Phenylamino-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1256]

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§ [1257] To a tertahydrofuvan (3 mL) solution of (4-phenylamino-phenyl)-aestohydroximoyl chlorida (150 mg, 0.578 mmo)l described in Mandacturing Example 13-1-3 was added triethylamine (201 µL, 1.44 mmo)). This mixture was stirred for 6.5 hours at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water and saturated aqueous sodium chlorids, died over anhydrous magnesium suffate, and filtered. The filtrate of was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ethy acetate = 1: -1 ethyl sectate) to totalin the title compound (107 mg, 52%).

14-NMR Spectrum (CDC)₃ 8 (ppm): 338 (2H, s), 4.55 (2H, brs), 5.34 (2H, brs), 5.96 (1H, brs), 5.91-5.94 (1H, mr), 7.24-7.28 (2H, mr), 7.24-7.28 (1H, mr), 7.24-7.28 (2H, mr), 7.2

45 [Example 130] 3-(3-(4-Butyl-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1258]

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H₂N NH₂

[1259] To a tetrahydroluran (3 m.l.) solution of (4-bulyt-phemyl)-excelohydrocimory) chloride (150 mg, 0.665 mmol) decribed in Manufacturing Example 70-1-3 and 3-ethymyl-pyridin-2,6-diamine (56.5 mg, 0.424 mmol) described in Manufacturing Example 13-1-3 was added triethyamine (232 µ.t., 1.66 mmol). This mixture was sizered for 5 hours at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dired over anthydrous magnesism sulfate, and filtered. The filterite was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ethyl acetate =1:1- ethyl acetate) to obtain the title compound (66 mo. 31 %).

¹H-NMR Spectrum (CDC_t) 3 (ppm): 0.90-0.94 (3H, m), 1.30-1.40 (2H, m), 1.55-1.62 (2H, m), 2.57-2.61 (2H, m), 3.98 (2H, s), 4.55 (1 H, brs), 5.34 (2H, brs), 5.91-5.93 (2H, m), 6.00 (1 H, s), 7.14 (2H, d, J = 8.0 Hz), 7.19(2H, d, J = 8.0 Hz), 7.48-7.50 (1H, m).

[Example 131] 3-(3-(6-(3-Fluoro-phenoxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1260]

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28 [1861] To a tetrahydrofuran (2 ml.) solution of 3-ethynyl-pyridin-2-8-diamine (10 mg, 75 µmol) described in Manufacturing Example 13-1-3 and (6-(3-fluoro-phenoxy)-pyridin-3-yl)-acetohydroximoyl chloride (42 mg, 0.15 mmol) described in Manufacturing Example 71-1-4 was added triethylamine (21 µL, 0.15 mmol), which was stirred for 1 hour at 50°C under nitrogen atmosphere. Water was added at room temperature to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueues sodium chloride, diried over anhydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: methanol = 20: 1) to obtain the title compound (27 mg, 95%).

¹H-NMR Spectrum (CDCl₃) δ (ppm):3.98 (2H, s), 4.57 (2H, s), 5.33 (2H, s), 5.94 (1 H, dd, J = 0.73, 8.2 Hz), 6.01 (1H, s), 6.86-6.94 (4H, m), 7.31-7.37 (1 H, m), 7.49 (1H, d, J = 8.4 Hz), 7.64 (1 H, dd, J = 2.6, 8.4 Hz), 8.15 (1H, d, J = 2.6 Hz).

[Example 132] 3-(3-(6-(4-Fluoro-phenoxymethyl)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1262]

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1263] To a methanol (5.00 mL) solution of 24-(4-fluoro-phenoxymethyl)-6-(2-fluorivolyly)-pyrisiane (5.00 mg, 0.181 mmol) described in Manufacturing Example 27-13 was acided filiabru methodic (13.7 mg, 0.382 mmol)under intrigen atmosphere, which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure, and anhydrous definitionmethane (4.00 mL) and analydrous tetrahydrofluora (2.00 mL), were added to the reaction. Trainium (VI) tetrachlorida (63.7 mg, 0.579 mmol) was added dropvies to the reaction mixture on a dry ice-drainol bisth (-78°C), after which the system was stirred for 40 minutes at 0°C. Water and ethyl acetate were added to the reaction mixture on an to be alth (0°C), and the organic layer was extracted with ethyl acetate. This organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under a reduced pressure to obtain a crude eroduct (4.30 mm.) To a tetrahydroflura (5.00 mL)

solution of 3-ethymyl-pyridin-2,6-diamine (4.00 mg, 0.030 mmol) described in Manufacturing Example 13-1-3 and his crude product (20.0 mg) was added triethylamine (12.5 µL, 0.030 mmol), which was strired for 2 hours at room temperature, whate was added to the reaction solution at room temperature, which was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by reverse-phase high performance liquid chromatography (using an acetontirile-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (1.53 mg, 25.4%) as a distributoreacetic acid selt.

MS mre (ESI) 392.18(MH+1)

Example 133] 3-(3-(4-Phenylaminomethyl-benzyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[1264]

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[1265] To a tetrahydroturan (3 mL) solution of (4-phenylaminomethyl-phenyly-bactohydroximoyl chlorids (150 mg, 0548 mmo)) described in Manufacturing Example 73-1-8 and 3-ethynyl-pyridin-2-6-diamine (46.4 mg, 0.348 mmo)) described in Manufacturing Example 13-1-3 was added triathylamine (104 µL, 0.748 mmo)). This mixture was stirred for 7 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, weaked with water, died over anhydrous magnesium suitles, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 1:1 10 to 1:2 ~ ethyl acetate) to lotatin the filtra compound (26 mg, 13%).

¹H-NMR Spectrum (CDCl₈) 8 (ppm); 4.00 (2H, s), 4.31 (2H, brs), 4.46 (2H, brs), 5.50 (2H, brs), 5.90 -5.92 (1 H, m), 5.99 (1 H, s), 6.82-6.84 (2H, m), 6.89-6.73 (1 H, m), 7.15-7.20 (2H, m), 7.25-7.27 (1H, m), 7.32-7.34 (2H, m), 7.47-7.49 (1 H, m), 112661 Note that it was not observed that proton on the amino group of PNNFCH2 appeared on the NMR chart.

[Example 134] 3-(3-(6-(2-Fluoro-phenoxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

5 [1267]

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[1268] To a mixture of (e-[2-fluoro-phenoxy)-pyridin-3-y)-acetohydroximoyl chioridia (28 mg) described in Manufacturing Example 74-14 and tetrahydroturan (1 mL) were added 3-ethynyl-pyridin-2-6-diemine (10 mg, 0.075 mmo)l described in Manufacturing Example 13-1-3 and infethylamine (21 µL, 0.15 mmol), which was stirred for 5 hours at room temperature. Water was added to the reaction mixture at the same temperature, which was extracted with ethyl acetata. The organic layer was washed with saturated aqueues osdium-chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate alone) to obtain the title compound (13 mo. 45%).

¹H·NMR Spectrum (CDCl₃) δ (ppm): 3.96 (2H, s), 4.50 (2H, br s), 5.27 (2H, br s), 5.93 (1 H, d, J = 8.4 Hz), 5.99 (1 H, s), 6.96 (1 H, d, J=8.6 Hz), 7.16-7.23 (4H, m), 7.48 (1 H, d, J=8.2 Hz), 7.62 (1 H, dd, J=2.6, 8.4 Hz), 8.08 (1 H, d, J=2.6 Hz).

[Example 135] 3-(3-(6-(4-Fluoro-phenoxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1269]

[1270] To a mixture of (6:(4-fluoro-phenoxy)-pyridin-3-yl-seetohydroximoyl chloride (25 mg) described in Manufacturing Example 75-1-4 and tetrahydroturan (1 mL) were added 3-ethynyl-pyridin-2,6-diamine (8 mg, 0.060 mmol) described in Manufacturing Example 13-1-3 and treithylamine (17 µL, 0.12 mmol), which was stirred for 6 hours at room temperature. Water was added to the reaction mixture at the same temperature, which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate) to obtain the title compound (8.7 mg,

TH-NMR Spectrum (DMSO-d₆) 6 (ppm): 3.95 (2H, s), 5.81 (2H, br.s), 5.83 (1 H, d, J = 8.4 Hz), 6.12 (2H, br.s), 6.41 (1 H, s), 7.00 (1 H, d, J = 8.4 Hz), 7.14-7.18 (2H, m), 7.21-7.26 (2H, m), 7.52 (1 H, d, J = 8.4 Hz), 7.78 (1 H, dd, J = 2.4, 8.4 Hz), 8.12 (1 H, d.1 - 2.4 Hz), 8.72 (1 H, d.1 - 2.4 Hz),

Example 136] 3-(3-(4-(Thiophen-3-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1271]

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[1272] To a tetrahydrofuran (3 mL) solution of (4-(thiophen-3-yhnethoxy)-phenyl)-esetohydroximoyl chloride (150 mg. 0.532 mmol) described in Manufacturing Example 77-14 and 3-ethynyl-pytidn-2-f-damine (452 g.g. 0.339 mmol) described in Manufacturing Example 13-1-3 was added triethylamine (165 μ L, 1.33 mmol). This reaction mixture was stimed for 1.5 hours at room temperature. This mixture was partitioned into eithyl acetate and water. The organic layer was separated, washed with water, dried over annyhous magnesium suitate, and filtered. The fiftrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 1:1 - ethyl acetate) to obtain the title compound (73 mg. 36%).

14-NMR Spectrum (DMSO-d₆) δ (ppm): 3.87 (2H, s), 5.06 (2H, s), 5.79 (2H, brs), 5.81-5.83 (1 H, m), 6.11 (2H, brs), 6.34 (1 H, s), 6.94-6.96 (2H, m), 7.15-7.17 (1 H, m), 7.20-7.22 (2H, m), 7.50-5.56 (3H, m).

[Example 137] 3-(3-(4-Cyclopentyloxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

⁵ [1273]

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[1274] To a tetrahydrofuran (3 mL) solution of (4-cyclopentyloxy-phenyl)-acetohydroximoyl chloride (150 mg, 0.592 mmol) described in Manufacturing Example 78-1-4 and 3-ethynyl-pyridin-2.6-diamine (50.3 mg, 0.378 mmol) described

in Manufacturing Example 13-1-3 was added triethylamine (206 μ L, 1.48 mmol). This reaction mixture was stirred for 1.5 hours at room temperature. This mixture was partitioned intently acetate and water. The organic blayer was separated, washed with water, died over anythous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH slike gel column chromatography (heptane: ethyl acetate = 1:1- ethyl acetate in child the title compound (F&m o.31 34).

¹I-I-NIM Spectrum (DMSO-d_b) 8 (ppm): 1.66-1.58 (2H, m), 1.87-1.88 (4H, m), 1.88-1.89 (2H, m), 3.86 (2H, s), 4.76-4.77 (1H, m), 5.79 (2H, brs), 5.81-5.84 (1H, m), 6.10 (2H, brs), 6.34 (1H, s), 6.82-6.84 (2H, m), 7.17-7.19 (2H, m), 7.50-7.52 (1H, m), 6.71 (2H, m), 7.17-7.19 (2H, m), 7.50-7.52 (1H, m), 7.17-7.19 (2H, m), 7.50-7.52 (1H, m), 7.50-7.52 (1

© [Example 138] 3-(3-(4-(Pyridin-3-yloxy)-benzyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[1275]

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[1276] To a methanol (1,0,0 mL) solution of 34-(4-2-hitro-ethyl)-phenoxyl-pyridine (618 mg, 3.58 mmol) described in Manufacturing Example 78-1-3 was added lithium methoide (254 mg, 6.70 mmol), which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure, and anhydrous dichloromethane (15.5 mL) and anhydrous tetrahydroturan (7.00 mL) were added to the residue. Titanium (V) her the reaction mixture on a dry loe-ethanol bath (-78°C) methor the reaction mixture was stirred for 30 minutes at room temperature. Aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture was stirred for 30 minutes at room temperature. Aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture on an inclusive or an i

¹H-NMR Spectrum (CD₃OD) δ (ppm): 3.96 (2H, s), 5.81 (2H, brs), 5.84 (1 H, d, J = 8.4 Hz), 6.12 (2H, brs), 6.40 (1 H, s), 7.04 (2H, d, J = 8.8 Hz), 7.36 (2H, d, J = 8.8 Hz), 7.40-7.42 (2H, m), 7.53 (1 H, d, J = 8.4 Hz), 8.35-8.38 (2H, m).

[Example 139] 3-(3-(4-Cyclohexyloxy-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1277]

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[1278] To a tetrahydrofuran (3 mL) solution of (4-cycloheayloxy-phenyl)-eactohydroximoyl chlorida (150 mg, 0.56 mmo) described in Manufacturing Example 79-14 and 3-sthynyl-prighdine-2,6-diamine (47.6 mg, 0.357 mmo) described in Manufacturing Example 13-13 was added triethylamine (195 µL, 1.4 mmo). This reaction mixture was selfred for 4 hours at room temperature. This institure was selfred through the catellate and water. The organic laver was separated.

washed with water, dried with anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH i silica get column chromatography (heptane: ethyl acetate =1:1~ ethyl acetate) to obtain the title comound (63 ma. 41%).

¹H-NMR Spectrum (CDCl₃) 8 (ppm): 1.24-1.41 (3H, m), 1.46-1.52 (3H, m), 1.79-1.80 (2H, m), 1.97-1.99 (2H, m), 3.94 (2H, s), 4.18-4.24 (1 H, b), 4.46 (2H, brs), 5.25 (2H, brs), 5.90-5.93 (1 H, m), 6.00 (1 H, s), 6.84-6.86 (2H, m), 7.16-7.18 (2H, m), 7.47-7.49 (1 H, m).

[Example 140] 3-(3-(4-(2-Furan-2-yl-ethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1279]

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[1280] To a mixture of (4(2-turan-2-yt-ethylphereyl)-acotohydroximoyl chloride (100 mg, 0.38 mmol) described in Manufacturing Example 80-17 and tetrahydrofuran (3 mL) were acided 3 ethynyl-pyrdin-2,6-diamine (25.3 mg, 0.19 mmol) described in Manufacturing Example 13-13 and triethylamine (0.1 mL, 0.76 mmol), which was stirred for 2 hours at room temperature. Water and ethyl acotate were added to the reaction mixture, and the organic layer was separated. This organic layer was washed with water and saturated aqueous socium chloride and ratio dover antydrous magnesium sulfate, and the solvent was everyorated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acotate : heptane = 1: 1 then ethyl acotate) to obtain the title compound (50 mg, 72%). 14-NMR Spectrum (CDC)₈ 3 (gpm): 2.88-2.88 (4H, m), 3.98 (2H, s), 4.47 (2H, brs), 5.52 (2H, brs), 5.51 (1 H, d, J = 8.4 Hz), 5.97 (1 H, d, J = 3.2 Hz), 5.99 (1 H, s), 6.27 (1 H, dd, J = 2.0, 3.2 Hz), 7.13 (2H, d, J = 8.0 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.31 (1 H, J, J = 8.0 Hz), 7.31 (2H, J = 8.0 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.33 (1 H, J, J = 8.0 Hz), 7.33 (1 H, J, J = 8.0 Hz), 7.33 (1 H, J, J = 8.0 Hz), 7.34 (1 H, J, J = 8.0 Hz), 7.34 (1 H, J, J = 8.0 Hz), 7.34 (1 H, J = 8.0 Hz), 7.35 (2H, brs), 5.35 (2H, brs), 5

[Example 141] 3-(3-(4-(4-Fluoro-phenoxy)-benzyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[1281]

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[1282] To a tetrahydrofuran (5.00 mL) solution of (4-(4-fluor-phenoxy)-phenyl)-acotohydroximoy) chloride (280 mg. 1.04 mmol) desoribed in Manufacturing Example 141-13 and 3-ethynyl-pridine-2,6-dismine (40.0 mg. 0.300 mmol) desoribed in Manufacturing Example 131-13 was added triethylamine (105 µL, 0.750 mmol) under nitrogen atmosphere at room temperature, which was stirred for 16 hours at room temperature. Water was added at room temperature to the reaction solution at room temperature to the reaction solution at room temperature, which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica eggle tolumn chromatography (ethyl acetate: heptane =3:1-) ethyl acetate to obtain the title compound (38.1 mc. 33.7%)

1H-MMR Spectrum (DMSO-d_d) 6 (ppm): 3.94 (2H, s), 5.81 (2H, brs), 5.83 (1H, d, J = 8.0 Hz), 6.12 (2H, brs), 6.39 (1 H, s), 6.39 (2H, d, J = 8.4 Hz), 7.03-7.08 (2H, m), 7.19-7.24 (2H, m), 7.31 (2H, d, J = 8.4 Hz), 7.52 (1H, d, J = 8.0 Hz). 17.821 The starting material, 44-4 (Juoro-phenoxy)-phenyl-acetohydroximov (bioloide, was swithestized as follows.

[Manufacturing Example 141-1-1] 4-(4-Fluoro-phenoxy)-benzaldehyde

[1284]

[1285] To an N,N-cimethylformamide (40.0 m.l.) solution of 4-fluorophenol (5.00 g, 44.6 mmol) and 4-fluorobenzaide-hyde (4.00 mg, 32.2 mmol) was added potassium carbonate (13.4 g, 96.6 mmol), which was stirred for 21 hours at 80°C. The reactions oldition was then code for room temperature, water was added thereto, and the reaction solution was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was everporated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : hebratan = 1; 156 – 1; 10) to obtain the title compound (6.00 g, 9.0 %).

¹H-NMR Spectrum (CDCl₃) δ (ppm) : 7.02-7.11 (6H, m), 7.85 (2H, d, J = 8.8 Hz), 9.91 (1H, s).

[Manufacturing Example 141-1-2] 4-(4-Fluoro-phenoxy)-1-(2-nitro-ethyl)-benzene

[1286]

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[1287] To an acetic acid (30.0 m.l.) solution of 4-(4-fluoro-phenoxy)-benzaldehylde (3.00g, 48.4 mmol) described in Manufacturing Example 141-1-1 were added nitromethane (4.03 g, 68.0 mmol) and ammonium acetate (2.03 g, 28.4 mmol) under nitrogen atmosphere at room temperature, which was stirred for 4 hours at 10°C. Water and erryl acetate were added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was vashed with water and a saturated ageous sodium choinde, died over enhytrious magnesium sulfate, and fifteed. The fiftire was concentrated under a reduced pressure, which gave a crude product (3.4 g). To a dimethyl sulfoxide (30.0 m.l.) solution of this crude product (3.4 g) and acets caid (3.0 om.l.) was added sodum brothydride (759 mg, 21.0 mmol) at room temperature willor configurations, which was stirred for 30 minutes at room temperature. Water was then added dropwise at room temperature will be cooling appropriately, which was stirred for 30 minutes at room temperature. Water was then added regard a common temperature will be cooling appropriately actually acquired acquired acquired acquired acquired to the standard acquired ac

[Manufacturing Example 141-1-3] (4-(4-Fluoro-phenoxy)-phenyl)-acetohydroximoyl chloride

[1288]

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[1289] To a methanol (2.00 mL) solution of 44.4-fluoro-phenoxy)-1-(2-nitro-ethyl)-benzene (500 mg, 1.91 mmol) desorbed in Manufacturing Example 14-11-2 was added tilhium methoxide (145 mg, 3.82 mmol) under nitrogen atmosphere at room temperature, which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure, and anhydrous dichloromethane (2.00 mL) and anhydrous tetrahydrofuran (5.00 mL) were added to the residue. Tilanium (10) (chloride (625 Hz, 478 mmol) was added dropwise to the reaction mixture on a dry ice-ethanol bath (-78°C), after which the system was stirred for 30 minutes at room temperature. Ware and ethyl acotate were added to the reaction mixture on an ice bath (0°C), and the orangic laver was separated. The orangic laver

washed with water and saturated aqueous sodium chloride, dried with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under a reduced pressure to obtain the filte compound (50 mg, 93 f6/s). ¹I-I-NIM Spectrum (DMSO-d₀) δ (ppm): 3.80 (2H, s), 6.96-6.97 (2H, m), 7.06-7.08 (2H, m), 7.21-7.27 (4H, m), 11.73 (1H, s).

[Example 142] 3-(3-(4-(3-Fluoro-phenoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1290]

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HAN N NH2

[1231] To a tetrahydrofuran (5.00 mL) solution of (4-(3-fution-o-phenoxy)-phenyl)-acetohydrox/moyl chloride [210 mg, 0.622 mmol) described in Manufacturing Example 81-1-2 and 3-ethynyl-pyridine-2,6-diamine (30.0 mg, 0.225 mmol) described in Manufacturing Example 13-1-3 was added triethylamine (94.1 µL, 0.675 mmol) at room temperature, which was strired for 30 minutes at room temperature. Water was added to the reaction solution at room temperature, which was extracted with ethyl acetate. The organic layer washed with saturated aqueous solution chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 2 : 1) to obtain the title compound (29.0 mg, 34.2%).

11-NMR Spectrum (DMSO-d₂) 5 (ppm): 3.37 (2H, s), 8.81 (2H, bm), 5.84 (1 H, d, J = 8.4 Hz), 6.12 (2H, bm), 6.84 Hz), 7.36 (2H, d, J = 8.4 Hz), 7.36 (2H, d, J = 8.4 Hz), 7.36 (2H, d, J = 8.4 Hz), 7.37 (2H, d, J = 8.4 Hz), 7.36 (2H, d, J = 8.4 Hz), 7.36

[Example 143] 3-(3-(4-(2-(Tetrahydrofuran-2-yl)-ethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1292]

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N N

[1283] To a mixture of (4-(2-tertar)ydrofuran-2-yterthyl-phenyl)-acetohydroxinnyd chlorida (145 mg. 0.54 mmo) described in Manufacturing Example 32-14 and tetrahydrofuran (3 ml.) were added 3-tethynyl-pyridin-2,6-d rainin (36 mg. 0.27 mmo)) described in Manufacturing Example 13-1-3 and triethylamine (0.15 ml., 1.08 mmo), which was stirred for 2 hours at room temperature. Water and ethyl acetate were added to the reaction mixture, and the organic layer was separated. This organic layer was washed with water and astrutated aqueous sodium chloride and dired over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica elocium chromatography (ethyl acetate : heptane = 1:1 then ethyl acetate) to obtain the title compound (76 mg. 77%). "H-NMR Spectrum (CDCl₃) 5 (ppm): 1.40-1.55 (H, m), 1.70-2.00 (SH, m), 2.60-2.80 (2H, m), 3.70-3.90 (3H, m), 3.70-3.9

[Example 144] 3-(3-(4-(2-Fluoro-phenoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1294]

19 [1295] To a tetrahydrofuvan (5.00 m.l.) solution of (4/2-fluoro-phenoxy)-phenyl)-scelohydrox/moyl chloride (210 mg. 0.622 mmol) described in Manufacturing Example 183-1-3 and 3 ethynyl-pyridin-2,6-diamine (30.0 mg. 0.225 mmol) described in Manufacturing Example 183-1-3 was added thethylamine (94.1 pt.L. 0.675 mmol) at room temperature, which was estimed for 16 hours at room temperature. Water was added at room temperature to the reaction solution at room temperature, which was extracted with ethyl acetate. The organic layer washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 2 : 1) to obtain the title compound (41.7 mg. 49.2%).

1H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.94 (2H, s), 5.81 (2H, brs), 5.82-5.85 (1H, m), 6.12 (2H, brs), 6.39 (1H, s), 6.92-6.95 (2H, m), 7.13-7.24 (3H, m), 7.30-7.32 (2H, m), 7.35-7.41 (1 H, m), 7.51-7.54 (1 H, m).

[Example 145] 3-(3-(5-Phenoxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[1296]

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[1237] To a methanol (6 mL) solution of 3-(2-nitro-ethyl)-5-phenoxy-pyridine (210 mg, 0.880 mmol) described in Mandracturing Example 145-1-4 was added lithium methoxide (86 mg, 1.72 mmol), which was stimed for 56 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. To a suspension of this residue in tetrahydrotruns (5 mL) ad methylene chorids (6 mL) was added thainum (fv) tetractionide (236 µL, 2.15 mmol) under nitrogen atmosphere, which was stirred for 50 minutes at 0°C. Sodium hydrogencarbonate was added to the reaction mixture at 0°C, which was extracted with enthyl acetate. The organic layer was expanated, washed with saturated aqueous sodium chloride, dired over arhydrous magnetismus suffate, and filtered. The filtrate was concentrated under a reduced pressure. To a tetrahydrotruran (4 mL) solution of this residue were added 3-ethynyl-pyridin-2.6-diamine (15 mg, 0.11 mmol) described in Manufacturing Example 13-1-3 and riethylamine (240 µL, 1.72 mmol), which was settracted with ethyl catata. The organic layer was added to the reaction mixture at room temperature, which was extracted with ethyl catata. The organic layer was separated, washed with saturated aqueous sodium chloride, dired over anytrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by reverse-phase night performance fluid chromotography (using an acciontific water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (5.6 mg, 1.1%) as a ditrifluoroacetic acid salt.

[1298] The starting material, 3-(2-nitro-ethyl)-5-phenoxy-pyridine, was synthesized as follows.

[Manufacturing Example 145-1-1] 5-Phenoxy-nicotinic acid methyl ester

[1299]

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10 [1300] To a solution of 5-hydroxy-ricotinic acid methyl ester (803 mg, 5.90 mmol) in tetrahydrofuran (10 mL) and N, N-dimethylformanide (10 mL) were added diphenyliodonium chloride (1.87 g, 5.90 mmol) and potassium r*butoxide (862 mg, 5.90 mmol) at 0°C, which was stirred for 2 hours and 30 minutes at room temperature. Water was added to the reaction mixture, which was extracted with ethyl accetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane : ethyl acetate

= 2 : 1) to obtain the title compound (1.11 g, 82%).

1H-NMR Spectrum (CDC₃) δ (ppm):3.93 (3H, s), 7.04-7.06(2H, m), 7.19-7.23 (1H, m), 7.39-7.43 (2H, m), 7.83 (1 H, dd, J = 1.7 2.9 Hz), 8.97 (1 H, d, J = 2.9 Hz), 8.95 (1 H, d, J = 1.7 Hz).

20 [Manufacturing Example 145-1-2] (5-Phenoxy-pyridin-3-yl)-methanol

[1301]

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1303] To a suspension of lithium aluminum hydride (680 mg, 14.5 mmol, purity :80%) in fatrahydrofuran (20 mL) was added 5-phenoxy-ricotinic acid methyl ester (1.11 g, 4.84 mmol) described in Manufacturing Example 145-11 at 0°C, which was strired for 20 minutes at room temperature. First water (689 µL), then a 5 N sodium hydroxide aqueous solution (689 µL), and then water (2.07 mL) were added at 0°C to the reaction mixture, which was filtered through a Cellite pad. The filtrate was concentrated under a reduced pressure, and the residue was printed by NH si flag el column chromatography (heptane : ethyl acetate = 1: 1) to obtain the title compound (756 mg, 78%).

H-HMR Spectrum (CCD4) & pomi): 777 (H, 1, 4 = 5.5 Hz, 3, 7.3 CH, 3, 5 = NHz, 7.3 CH, m), 7.15-7.19 (1)

H, m), 7.32-7.33 (1 H, m), 7.36-7.40 (2H, m), 8.33-8.34 (2H, m).

[Manufacturing Example 145-1-3] 5-Phenoxy-pyridine-3-carbaldehyde

[1303]

[1304] To a methylene chloride (20 ml.) solution of (5-phenoxy-pyridin-3-yl-)-methanol (756 mg, 3.76 mmol) described in Manufacturing Example 145-1-2 was added manganese(IV) dioxide (3.27 g, 3.76 mmol), which was sirred for 2 hours at room temperature. The insolubles were removed by filtrating through a Cellie pad, after which the filtrate was concentrated under a reduced pressure. The residue was purified by silice gel column chromatography (heptane: ethyl acetale = 2: 1 to 1: 1) to bottain the title compound (607 mg, 81 %).

1H-NMR Spectrum (CDCl₂) δ (ppm): 7.06-7.08 (2H, m), 7.22-7.26 (1H, m), 7.41-7.45 (2H, m), 7.64 (1 H, dd, J = 1.7, 2.9

Hz), 8.66 (1 H, d, J = 2.9 Hz), 8.79 (1 H, d, J = 1.7 Hz), 10.1(1H, s).

[Manufacturing Example 145-1-4] 3-(2-Nitro-ethyl)-5-phenoxy-pyridine

[1305]

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[1306] To an acetic acid (15 mL) solution of 5-phenoxy-pyridine-3-carbatkelpyla (607 mg, 3.05 mmol) described in Manufacturing Example 145-1-3 were added intromathen (826 µL, 15.3 mmol) and ammonium acetate (470 mg, 6.10 mmol), which was stirred for 3 hours at 100°C under nitrogen atmosphere. Water was added at room temperature to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueues oxidium chloride, dired over anhydrous magnesisms unsittee, and filtered. The filtrate was concentrated under a reduced pressure, To a solution of this residue in dimethyl suifoxide (10 mL) and aceta can be concentrated under a reduced pressure, To a solution of this residue in dimethyl suifoxide (10 mL) and aceta can be concentrated and water were added to the reaction mixture at room temperature while cooling appropriately, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium forlyding over anhydrous magnesium suitlets, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH isilica gel column chromatography (heptane: ethyl acetate = 1:1) to obtain the title commound (210 mg, 28%).

1H-NMR Spectrum (CDCi₃) δ (ppm);3.34 (2H, t, J = 6.8 Hz), 4.65 (2H, t, J = 6.8 Hz), 7.05-7.07 (2H, m), 7.28-7.32 (1 H, m), 7.38 (1 H, s), 7.44-7.48 (2H, m), 8.23-8.24 (2H, m).

[Example 146] 3-(3-(3-Pyridin-2-vl-benzyl)-isoxazol-5-vl)-pyridin-2.6-diamine

[1307]

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[1308]. To a mixture of (3-(pyridin-2-y)-phenyt)-acothyytroximoytohloride (50 mg) described in Nerutacturing Exemple 44-1-3 and tetrahydrofuran (2 mL) were added 3-ethynyt-pyridin-2,6-diamine (6.0 mg, 0.045 mmot) described in Manufacturing Example 13-1-3 and trierhytenine (38 µL, 0.27 mmot), which was suffered for 2 hours at room temperature. Water was added to the reaction mixture at the same temperature, which was extracted with ethyl acctate. The organic layer was washed with saturated aqueous sodium-chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate) to obtain the title compound in a crude product. Then, the residue was purified by reverse-phase high performance liquid chromatography (using an acciontifie-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (3.7 mg, 14%) as a ditrifluoroacetic acid salt.

MS m/e(ESI) 344.24(MH+)

[Example 147] 3-(3-Biphenyl-3-ylmethyl-isoxazol-5-yl)-pyridin-2,6-diamine

[1309]

[9 [1310] To a mixture of biphenyi-3-yi-ascelohydroximoyi chloride (60 mg) described in Manufacturing Example 65-1-3 and tetrahydrotruna (3 mt), were added 3-ethylwyptivdia-2.6 damine (15 mg), c11 mmol) described in Manufacturing Example 13-1-3 and triethylamine (94 μL, 0.68 mmol), which was stirred for 2 hours at room temperature. Water was added to the reachin mixture at the same temperature, which was extracted with ethyl acetate. The organic Islaw as washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by htt silica gel column chromatography (ethyl acetate) to obtain the title compound in a crude product. Then, the residue was purified by reverse-phase high performance (laud chromatography (using an acetothrile-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (32 mg, 62%) as a trifluoroacetic acid salt. MS my(ESS) 434.3 lB/MHY.

Example 148] 3-(3-(4-Phenoxymethyl-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1311]

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[1312] To a tetrahydrofurar (3 mL) solution of (4-phenoxymethyl-phenyl)-seaterhydroximoy chloridae (150 mg, 0.545 mmol) described in Manufacturing Example 86-1-5 and 3-sthynyl-gyidnia-26-diamle (463 mg, 0.348 mmol) described in Manufacturing Examples 13-1-3 was added triethylemine (104 µL, 0.747 mmol), which was stirred for 1 hour at room temperature. This mixture was partitioned into ethyl acteals and water. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium suttae, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetale) to obtain the title compound (45 mg, 225 mg.).

¹H -NMR Spectrum (CDCl₃) δ (ppm): 4.03 (2H, s), 4.46 (2H, brs), 5.05 (2H, s), 5.25(2H, brs), 5.91-5.93 (1 H, m), 5.99 (1 H, s), 6.97-6.99 (3H, m), 7.26-7.32 (4H, m), 7.40-7.42 (2H, m), 7.47-7.49 (1 H, m).

[Example 149] 3-(3-(4-(3-Fluoro-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

45 [1313]

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[1314] To a tetrahydrofuran (2 mL) solution of (4-(3-fluoro-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride (33 mg, 0.11 mmol) described in Manufacturing Example 149-1-4 were added 3-ethynyl-pyridin-2,6-diamine (10 mg, 75 mol) described in Manufacturing Example 13-3 and triethylmine (21 mL, 0.15 mmol), which was stirred for 2 hours

and 25 minutes at 50°C and under nitrogen atmosphere. Water was added to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: methanol = 20:1) to obtain the title commount (27 min. 3%).

14-14MR Spectrum (DMSO-d₂) δ (ppm):3.97 (2H, s), 5.23 (2H, s), 5.80 (2H, s), 5.83 (1 H, d, J = 8.4 Hz), 6.11 (2H, s), 6.39 (1 H, s), 7.35 (2H, d, J = 8.2 Hz), 7.39 (1 H, dd, J = 4.6, 8.2 Hz), 7.43 (2H, d, J = 8.2 Hz), 7.51 (1 H, d, J = 8.4 Hz), 7.66 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J = 1.6, 8.4 Hz), 7.86 (1 H, dd, J

[1315] The starting material, (4-(3-fluoro-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 149-1-112-(4-Bromo-benzyloxy)-3-fluoro-pyridine

[1316]

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5 [1317] To an N.N-dimethylformamide (15 mL) solution of (4-bromo-phenyl)-methanol (1.56 g, 8.34 mmol) was added sodium hydride (401 mg, 8.35 mmol, 50% in oll), which was stirred for 5 minutes at room temperature. Then, an N.N-dimethylformamide (5 mL) solution of 2-chitoro-3-fluoropyridine (967 mg, 7.35 mmol) was added to this mixture, which was stirred for 1 hour and 10 minutes at room temperature. Water was to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, died over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 2:1) to obtain the title compound (2.03 o, 98%).

¹H-NMR Spectrum (CDCi₃) δ (ppm):5.13 (2H, s), 7.17 (1 H, dd, J = 4.4, 8.1 Hz), 7.20 (1 H, dd, J = 2.0, 8.1 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.54 (2H, d, J = 8.4 Hz), 8.02 (1H, dd, J = 2.0, 4.4 Hz).

[Manufacturing Example 149-1-2] 4-(3-Fluoro-pyridin-2-yloxymethyl)-benzaldehyde

[1318]

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[1319] To a tetrahydrofuran (40 m.l.) solution of 2:44-bromo-benzyloxy)-3-fluoropyridine (2.03 g. 7:20 mmol) described in Marufacturing Example 149-1-1 was added ne Buyllstimin (5.0 km l. 1.6 M becane solution, 7:22 mmol) under introgen atmosphere at -78°C, which was stirred for 45 minutes at -78°C. Then, N,N-dimethylformamide (725 µL, 9.36 mmol) was added to the reaction mixture at -78°C, which was stirred for 1 hour and 10 minutes while the temperature was raised to room temperature. Water was added to the reaction solution at room temperature, which was extracted with ethyl acotate. The organic layer was separated, washed with saturated aqueous sodium chloride, dired over anhydrous mannesium sulfate, and filtered. The residue was purified by silica ed column chromatocarby threatane; ethil acetate

= 2:1) to obtain the title compound (887 mg, 53%).

¹H-NMR Spectrum (CDCl₃) δ (ppm):5.26 (2H, s), 7.17-7.26(2H, m), 7.64 (2H, d, J = 8.1 Hz), 7.94 (2H, d, J = 8.0 Hz), 8.05 (1 H, dd, J = 1.8, 4.4 Hz), 10.0 (1 H, s).

5 [Manufacturing Example 149-1-3] 3-Fluoro-2-(4-(2-nitro-ethyl)-benzyloxy)-pyridine

[1320]

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[1321] To an scelic said (20 mL) solution of 4-(3-fluoro-pyridin-2-yloxymethyl-benzaldehyde (887 mg, 3.84 mmol) described in Meuntachuring Example 149-1-2 482 were added intromethane (10 4m, 1.92 mmol) and armonium acetate (592 mg, 7.88 mmol), which was stirred under nitrogen atmosphere for 4 hours and 30 minutes at 100°C. Water was added to the reaction mixture at 0°C, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chhoride, dried over anhydrous magnesium sultete, and filtered. The filtrated was concentrated under a reduced pressure. To a solution of this residue in dimethyl sulfoxide (20 mL) and sectic acid (mL) was added sodium bronytide (231 mg, 7.88 mmol), which was sitrated for 30 minutes at room temperature. Sodium hydrogencarbonate and water were added to the reaction solution at room temperature while cooling appropriately, which was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chhoride, oried over analystowum angressium sulfete, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 2:1) to obtain the title compount (674 m. 6, 64%).

¹H-NMR Spectrum (CDCl₃) δ (ppm):3.33 (2H, t, J = 7.2 Hz), 4.62 (2H, t, J = 7.2 Hz), 5.15 (2H, s), 7.16 (1 H, dd, J = 4.8, 8.0 Hz), 7.20 (1 H, dd, J = 2.0, 8.0 Hz), 7.23-7.25 (2H, m), 7.41 (2H, d, J = 8.4 Hz), 8.00 (1H, dd, J = 1.6, 4.4 Hz).

[Manufacturing Example 149-1-4] (4-(3-Fluoro-pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride

[1322]

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HO N CI O N

[1323] To a methanol (10 mL) solution of 3-fluoro-2(4(2-0nitive-thyl)-benzyloxyl-pyridine (674 mg, 2.44 mmol) described in Manufacturing Example 149-1-3 was added lithium methoxide (185 mg, 4.87 mmol), which was stirred for 5 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. To a suspension of this residue in tetrahydrofuran (10 mL) and methylene chioride (10 mL) was added titanium (IV) tetrachioride (900 nL, 537 mmol) under nitrogen atmosphere at 7-87°C, which was stirred for 1 hour at 0°C. Water was added to the reaction mixture at 0°C, which was then extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chioride, dried over anhydrous magnesium sulfate, and then filtered with neutral silica gel. The filtrate was concentrated under a reduced pressure to obtain the title compound (629 mg, 88%). This compound was used in the following reaction without any further purification.

¹H-NMR Spectrum (CDCl₃) δ (ppm):3.82 (2H, s), 5.17 (2H, s), 7.17 (1 H, ddd, J = 0.4, 4.8, 8.0 Hz), 7.23 (1 H, dd, J = 1.6, 8.0 Hz), 7.32 (2H, d, J = 7.9 Hz), 7.43 (2H, d, J = 7.9 Hz), 7.64 (1 H, s), 8.01 (1 H, dd, J = 1.7, 4.6 Hz).

Example 150] 3-(3-(3-Fluoro-4-(pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1324]

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H,N N NH,

[1325] To a methanol (20.0 mL) solution of 2-(2-fluoro-4-(2-nitro-ethyl)-phenoxymethyl)-pyridine (500 mg. 1.81 mmol) described in Manufacturing Example 87-1-3 was added lithium methoxide (137 mg. 3.61 mmol) under nitrogen atmosphere, which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure, and dichloromethane (15.0 mL) and anhydrous tetrahydrofuran (7.00 mL) were added to the residue. Titanium (IV) chloride (656 μL, 5.97 mmol) was added dropwise to the reaction mixture on a dry ice-ethanol bath (-78°C), and which was stirred for 30 minutes at room temperature. Aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture on an ice bath (0°C), which was filtered through a Celite pad. The organic layer of the filtrate was extracted with ethyl acetate, and this organic layer was washed with water and saturated aqueous sodium chloride. dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain a crude product (300 mg). To a tetrahydrofuran (5.00 mL) solution of this crude product (150 mg) and 3-ethynyl-pyridin-2.6-diamine (30.0 mg, 0.225 mmol) described in Manufacturing Example 13-1-3 was added triethylamine (94.1 µL, 0.675 mmol) at room temperature, which was stirred for 1 hour at room temperature. Water was added to the reaction solution. which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 2 : 1 → 10 : 1) to obtain the title compound (35.0 mg, 39.7%).

14-NMR Spectrum (DMSO-d₀) δ (ppm): 3.90 (2H, s), 5.22 (2H, s), 5.80 (2H, brs), 5.83 (1 H, d, J = 8.8 Hz), 6.12 (2H, brs), 6.38 (1 H, s), 7.04 (1 H, d, J = 8.4 Hz), 7.15-7.23 (2H, m), 7.34-7.37 (1 H, m), 7.52 (2H, d, J = 8.0 Hz), 7.85 (1 H, d, J = 8.0 Hz), 8.68 (1 H, d, J = 8.0 Hz), 7.85 (

[Example 151] 3-(3-(4-(Thiazol-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

v [1326]

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[1327] To a letrallydrofuran (3 mL) solution of 44;6-[2,6-diamino-pyridin-3-yh]-isoxazol-3-yimethy)-phenol (50 mg, 0.18 mmol) described in Manufacturing Example 18-1-1 was added a 5 N sodium hydroxide aqueous solution (35.4 µL, 0.18 mmol), which was dissolved by irraditating ultrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white solid. To a suspension of this solid in NN-dimethyformamide (1 mL) was added an NN-dimethyformamide (1 mL) solution of 2-chloromethy-filazole (28.8 mg, 0.21 mmol) described in manufacturing Example 88-1-2, which was stirred for 3 hours at 60°C. The reaction mixture was cooled to room temperature and then partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dired over anthythours manuselum stuffe, and filtered. The filtrate was concentrated under a reduced

pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate) to obtain the title compound (43.0 mg, 64%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.89 (2H, s), 5.41 (2H, s), 5.79 (2H, brs), 5.82 (1 H, d, J = 8.8 Hz), 6.11 (2H, brs), 6.55 (1 H, s), 7.01 (2H, d, J = 8.8 Hz), 7.24 (2H, d, J = 8.8 Hz), 7.51 (1 H, d, J = 8.4 Hz), 7.77 (1 H, d, J = 3.6 Hz), 7.83 (1 H, d, J = 3.2 Hz).

[Example 152] 3-(3-(6-(3,4-Difluoro-benzyloxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1328]

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[1329] The title compound (90 mg, 73%) was obtained according to the method similar to those of Example 3, using 3-ethynyl-pyridin-2,6-diamine (40 mg, 0.30 mmol) described in Manufacturing Example 13-1-3 and (6-(3,4-difluorobenzyloxy)-pyridin-3-yll-acetohydroximoyl chloride (140 mg, 0.45 mmol) described in Manufacturing Example 89-1-1. H-MMR Spectrum (DMSO-dg) δ (ppm): 3.92 (2H, s), 5.31 (2H, s), 5.31 (2H, brs), 5.33 (1H, dd, J = 1.6, 8.0 Hz), 6.12 (2H, brs), 6.40 (1H, d, J = 1.6, Hz), 6.86 (1 H, d, J = 8.0 Hz), 7.28-7.34 (1 H, m), 7.39-7.47 (1H, m), 7.48-7.56 (2H, m), 7.55-7.70 (1H, m), 8.14 (1H, s).

[Example 153] 3-(3-(6-(2,4-Difluoro-benzyloxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[1330]

[1331] The title compound (62 mg, 67%) was obtained according to the method similar to those of Example 12, using 3-ethynyl-pyridin-2-6-diamine (30 mg, 0.23 mmol) described in Manufacturing Example 13-13 and (6-t2.4-dilluor-benzyloxyl-pyridin-3-yl-pectohyridin-yllor) collision (10 mg, 0.34 mmol) described in Manufacturing Example 90-1-1. H-NMR Spectrum (DMSO-d₀) 6 (ppm): 3.92 (2H, s), 5.34 (2H, s), 5.81 (2H, brs), 5.33 (1H, d, J = 8.0 Hz), 6.12 (2H, brs), 6.34 (1H, s), 6.83 (1H, d, J = 8.0 Hz), 7.56-7.84 (1H, m), 7.66 (1H, dd, J = 2.0 Hz), 8.11 (2H, d, J = 2.0 Hz).

(5 [Example 154] 3-(3-(6-(Pyridin-2-yloxymethyl)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1332]

[1333] To a tetrahydrofuran (2 mL) solution of (6-(pyridin-2-yloxymethyl)-pyridin-3-yl)-acetohydroximoyl chloride (24

mg) described in Manufacturing Example 154-1-8 were added 3-ethynyl-pyridin-2,6-diamine (5.0 mg, 38 µmol) described in Manufacturing Example 134-13 and triethylamine (13 µL, 94 µmol), which was stirred for 1 hour at 50°C. Water was added to the reaction mixture, which was extracted with eithyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: methanol = 20: 11 to obtain the title compound (2.2 mg, 58°N).

11-1MR Spectrum (CDL) ô (ppm):4.03 (2H, s), 4.53 (2H, s), 5.28 (2H, s), 5.50 (2H, s), 5.82 (1 H, d, J = 8.4 Hz), 6.00 (1 H, s), 8.85-6.91 (2H, m), 7.43 (1 H, d, J = 7.9 Hz), 7.47 (1 H, d, J = 8.4 Hz), 7.58-7.62 (2H, m), 8.14-8.16 (1 H, m), 8.58 (1 H, d, J = 2.4 Hz).

[1334] The starting material, (6-(pyridin-2-yloxymethyl)-pyridin-3-yl)acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 154-1-1] 6-Bromo-pyridine-3-carbaldehyde

[1335]

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[1338] To a diethyl ether (80 mL) solution of 2,5-dibromopyridine (3.00 g, 12.7 mmol) was added *n*-buryl lithium (7.99 mL, 1.8 M hexane solution, 12.7 mmol) under nitrogen atmosphere at -78°C, which was stirred for 50 minutes at -78°C. Then, NN-dimethylformamide (1.1 mL, 15.2 mmol) was added to the mixture, which was stirred for 55 minutes while the temperature was raised to room temperature. Water was added to the reaction solution at morn temperature, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chhoride, dried over anhydrous magnesium sullate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 3: 1) to obtain the title compound (1.5 a. d.68%).

¹H-NMR Spectrum (CDCl₃) δ (ppm):7.69 (1H, dd, J = 0.73, 8.2 Hz), 8.03 (1H, dd, J = 2.4, 8.2 Hz), 8.84 (1 H, dd, J = 0.73, 2.4 Hz), 10.1 (1H, s).

[Manufacturing Example 154-1-2] 2-Bromo-5-[1,3]dioxolan-2-yl-pyridine

[1337]

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[1338] To a toluene (100 ml.) solution of 6 hormon-pyridine-3-carbaldehyde (5.0.9, 27 mmol) described in Manufacturing Example 164-11 were added eithylene glycol (3 on ml., 64 mmol) and p-louenesulforie acid monehydrate fol 12 mg. 2.7 mmol), which was refluxed for 3 hours and 40 minutes under nitrogen atmosphere. Sodium hydrogencerbonate and water were added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, effect over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane : ethly acetate = 1; 10 to obtain the filte compound (6.0, 9.7%).

 1 H-NMR Spectrum (CDCl₃) δ (ppm):4.03-4.13 (4H, m), 5.83(1H, s), 7.49-7.52 (1H, m), 7.64-7.67 (1 H, m), 8.46 (1 H, d, J = 2.4 Hz).

[Manufacturing Example 154-1-3] 5-[1.3]Dioxolan-2-vl-pvridine-2-carbaldehyde

[1339]

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[1340] To a tetrahydrofuran (100 mL) solution of 2-bromo-5f (1.3)dioxolan-2-y-f-pyridine (4.7 or, 2.0.7 mmol) described in Manufacturing Example 154-1-2 was added n-butyl fithium (14.3 mL, 1.6 M hexane solution, 2.2.8 mmol) under nitrogen stroosphere at -78°C, which was stirred for 20 minutes at -78°C. Then, NN-dimethylformamide (1.92 mL, 24.8 mmol) was added to the reaction mixture, which was estimated to the preaction mixture, which was estimated with ethyl acetaet. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered.
The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heatine); ethil acetaet 2.1 to obtain the title compound (1.7 a. 4.7%).

¹H-NMR Spectrum (CDCl₂) δ (ppm):4.07-4.16 (4H, m), 5.94(1H, s), 7.98 (2H, s), 8.88 (1 H, s), 10.1 (1H,s).

[Manufacturing Example 154-1-4] (5-[1,3]Dioxolan-2-vi-pvridin-2-vi)-methanol

[1341]

O OHO

[1342] To an ethanol (20 mL) and ternalydrofuran (20 mL) solution of 5-[1,3]dioxolan-2y-lsyntiine-2-carbaidehyde (1.73 g., 9.66 mmol) described in Manufacturing Example 154-13 was added sodium borohydride (731 mg, 19.3 mmol), which was sirred for 25 minutes at room temperature. Water was added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhylous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and he residue was purified by silica gel column chromatography (heptane: ethyl acetale = 1:2) to obtain the title compound (1.37 g. 78%). **
14-NMR Spectrum (CDCL) 8 (ppm):3.65 (14, s), 4.05-4.1644, m), 4.78 (24, s), 5.87 (14, s), 7.26-7.28 (14, m), 7.80 (14, d.) = 2.0, 8.1 Hz), 8.85 (14, d.) = 2.0 Hz).

[Manufacturing Example 154-1-5] 5-[1,3]Dioxolan-2-yl-2-(pyridin-2-yloxymethyl)-pyridine

[1343]

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[1344] To an NN-dimetrylformamide (40 mL) solution of (5+1.3)dioxolan-2-yl-prydin-2-yl)-methano (1,37 g. 7.56 mmo) described in Manufacturing Example 154-1-4 was added sodium hydride (333 mg. 8.32 mmol, 60% in oil), which was stirred for 6 minutes at 0°C. Next, 2-fluoropyrdine (716 p.L., 8.32 mmol) was added to the reaction mixture, which was stirred for 46 minutes at 50°C. Water was added to the reaction mixture at norm temperature, which was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous megnesium sultate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by slica gel column chromatography (heptane : ethyl acetate = 2:1 to 1:1) to obtain the title compound (1.51 a. 77%).

¹H-NMR Spectrum (CDCl₃) δ (ppm):4.04-4.15 (4H, m), 5.53(2H, s), 5.87 (1H, s), 6.86-6.91 (2H, m), 7.47 (1 H, d, J = 8.1 Hz), 7.58-7.63 (1 H, m), 7.79 (1 H, dd, J = 2.0, 8.2 Hz), 8.14-8.16 (1 H, m), 8.70 (1 H, d, J = 2.0 Hz).

[Manufacturing Example 154-1-6] 6-(Pyridin-2-yloxymethyl)-pyridine-3-carbaldehyde

25 [1345]

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[1346] To a solution of 5-[1,3]dioxolan-2-yi-2-(pyridin-2-yloxymethyl)-pyridine (1.51 g, 5.85 mmol) described in Manutacturing Example 154-1-5 in tetrahydrofuzina (15 mL) and dimethyl sulfoxide (10 mL) was added a 5 N hydrochloric acid aqueous solution (3 mL), which was stirred for 25 minutes at room temperature, end then for another 1 hour at 20 minutes at 60°C. A 5 N sodium hydroxide aqueous solution was edded to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by slica gel column chromatography (heptane: ethyl acetate =1:1) to obtain the title compound (603 ma. 48%).

 1 H-NMR Spectrum (CDCl₃) δ (ppm):5.61 (2H, s), 6.90-6.94(2H, m), 7.26-7.66 (2H, m), 8.12-8.14 (1 H, m), 8.17 (1 H, dd, J = 2.0.8.1 Hz), 9.05 (1 H, d, J = 1.7 Hz), 10.1 (1H, s).

[Manufacturing Example 154-1-7] 5-(2-Nitro-ethyl)-2-(pyridin-2-yloxymethyl)-pyridine

[1347]

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[1348]. To an acetic acid (20 mL) solution of 6-(pyridine-2-yloxymethyl-pyridine-3-carbatichyde (504 mg, 2.35 mmo) described in Mennfacturing Example 1541-18 were acided nitronethern (635 gL.11 at mmo) and ammonium acetate (383 mg, 4.71 mmo), which was stitred for 4 hours at 100°C under nitrogen atmosphere. Water was acided to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was separated, weathed with structured queue so sodium-holforide, field over any though structured support. The filtrate was concentrated under a reduced pressure. To a solution of this residue in dimetryl sulfordic (25 mL) and acetic acid (2,5 mL) was added solum broxydyride (178 mg, 4.71 mmo), which was stred for 25 minutes at room temperature. Sodium hydrogenera-bonate and water were added to the reaction mixture at room temperature, which was extracted with ethyl scetter. The organic layer was separated, washed with saturated aqueous sodium-toninde, dired over anylydous magnesium-sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (hepsare : eithyl acetate = 1:1) to obtain the title compound (38 mg, 15%).

¹H-NMR Spectrum (CDCl₃) δ (ppm):3.38 (2H, t, J = 6.8 Hz), 4.66 (2H, t, J = 6.8 Hz), 5.83 (2H, s), 6.90-6.96 (2H, m), 7.63-7.70 (2H, m), 7.78 (1H, dd, J = 1.6, 8.0 Hz), 8.14 (1H, dd, J = 1.6, 4.8 Hz), 8.68 (1H, d, J = 1.2 Hz).

[Manufacturing Example 154-1-8] (6-(Pyridin-2-yloxymethyl)-pyridin-3-yl)-acetohydroximoyl chloride

[1349]

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[1350] To a methanol (5 mL) solution of 5-(2-nitro-ethy)-2-(pyridin-2-yloxymethyl)-pyridine (93 mg, 0.36 mmol) described in Manufacturing Example 154-1-7 was added lithium methodide (27 mg, 0.72 mmol), which was stirred for 5 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure. To a suspension of this residue in tetrahydrofuran (3 mL), and methylene chloride (3 mL) was added thanium (IV) tetrachloride (67 mL, 0.79 mmol) under nitrogen atmosphere at -78°C, which was stirred for 2 hours at 0°C. Worth stimuline (1) tetrachloride (60 mL), 0.46 mmol) was added at -78°C, which was stirred for 3 hours at 0°C. Water was added to the reaction mixture at 0°C, which was then extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (24 mg). This compound was used in the following reaction without any further purification.

[Example 155] 3-(3-(5-(4-Fluoro-phenoxy-thiophen-2-v/methyl)-isoxazol-5-vl)-pyridin-2.6-diamine

[1351]

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[1382] To a tetrahydrofuran (5.00 mL) solution of (5-(4-fluore-phenoxy)-hilophen-2-yl)-acetohydroximoyi chioride (250 mg, 0.876 mmol) described in Manufacturing Example 91-1-4 and 3 ethynly-pyridin 2-6 diamine (6.0 mg, 0.376 mmol) described in Manufacturing Example 13-1-3 was added to the thylamine (157 μL, 1.27 mmol) at room temperature, which was stirred for 3 hours at 60°C. Water was added to the reaction mixture in room temperature, which was stirred for 3 hours at 60°C. Water was added to the reaction mixture in room temperature, which was extracted with erthy decates. The organic layer was washed with saturated aqueous sodium chloride and dried over an hydrous magning in suitate, and the solvent was eveporated under a reduced pressure. The residue was purified by NH silica gel column chromotography (ethyl acetate: heptane 2: 1 - 3: 1) to obtain the title compound (20.9 mg, 14.5%). ¹¹I-I-IMR Spectrum (DMSO-d₂) δ (ppm); 4.09 (2H, s), 5.82 (2H, bm.), 5.84 (1H, d, J = 8.4 Hz), 6.14 (2H, bm.); 6.75 (1H, d, J = 8.4 Hz), 6.14 (2H, m.), 7.19-7.26 (2H, m.), 7.19-7.26

[Example 156] 3-(3-(5-(4-Methyl-benzyl)-thiophen-2-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1353]

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[1354] To a tetrahydroman (5.00 mL) solution of (5-(4-methy-benzyl)-thiophen-2-yl)acetohydroxinoyi chlorida (250 mg, 0.884 mnol) described in Manufacturing Example 92-1-5 and 3-thyryl-yydridn-2, 6-damine (5.00 mg, 0.376 mnol) described in Manufacturing trample 13-1-3 was added thethylamine (157 µL, 1.13 mmol) at room temperature, which was stirred for 30 minuses at 60°C. Water was added to the reaction solution at room temperature, which was extracted with ethyl acetale. The organic layer was weathed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was everporated under a reduced pressure. The residue was purified by NH silica el column chromotography (lethyl sectate: heptens = 2:1 -3 -3; 10 to obtain the title compound (4.98 mg, 352%). 11-NMR Spectrum (DMSO-d₀) 5 (ppm): 2.25 (SH, s), 4.01 (2H, s), 4.07 (2H, s), 5.80 (2H, brs), 6.83 (1 H, d, J = 8.4 Hz). (31 (2+, brs), 3.93 (H, s), 6.80 (H, d, J = 8.2 Hz), 76 (H, d, J = 8.2 Hz), 70.8-71 (4+, m), 8.00 (H, d, J = 8.4 Hz).

[Example 157] 3-(3-(3-Fluoro-4-(5-fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1355]

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[1356] To a tetrahydroturan (5.00 m.), solution of (3-fluoro-4-(5-fluoro-pyridin-2-ylnethoxy)-phenyl)-acetohydroximoyl chloride (170 mg. 0.554 mmol) described in Manufacturing Example 94-1-3 and 3-ethynyl-pyridin-2,6-diamline (40.0 mg. 0.300 mmol) described in Manufacturing Example 13-1-3 was added triethylamline (125 μ.L, 0.300 mmol) at room temperature, which was stirred for 30 minutes at room temperature. Water was added to the reaction solution at room temperature, which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium choride and dried over anhydrous magnesium suitate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 2:1 - 3:1) to obtain the title commount (50 on w. 48.0%).

1H-NMR Spectrum (DMSO- d_0) δ (ppm) : 3.90 (2H, s), 5.22 (2H, s), 5.80 (2H, brs), 5.83 (1 H, d, J = 8.4 Hz), 6.11 (1 H, brs), 6.38 (1 H, s), 7.05 (1 H, d, J = 8.4 Hz), 7.19-7.22 (2H, m), 7.51 (2H, d, J = 8.4 Hz), 7.59-7.62 (1 H, m), 7.76-7.81 (1 H, m), 8.58 (1 H, d, J = 2.8 Hz), [Example 158] 3-(3-(2-Fluoro-4-(pyridin-2-ylmethoxy)-benzyl)-isoxazoi-5-yl)-pyridin-2-6-diamine

[1357] To a methanol (20.0 mL) solution of 2-(3-fluoro-4-(2-nitro-ethyl)-phenoxymethyl)-pyridine (400 mg, 1,45 mmol) described in Manufacturing Example 95-1-3 was added lithium methoxide (110 mg, 2.90 mmol), which was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under a reduced pressure, and anhydrous dichloromethane (20.0 mL) and anhydrous tetrahydrofuran (10.0 mL) were added to the residue. Titanium (IV) chloride (510 µL, 4.64 mmof) was added dropwise to the reaction mixture on a dry ice-ethanol bath (-78°C), which was stirred for 60 minutes at room temperature. Water, ethyl acetate, and tetrahydrofuran were added to the reaction mixture on an ice bath (0°C), and the organic layer was extracted with ethyl acetate. This organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and then filtrate was concentrated under a reduced pressure to obtain a crude product (360 mg). To a tetrahydrofuran (5.00 mL) solution of 3ethynyl-pyridin-2,6-diamine (40.0 mg, 0.300 mmol) described in Manufacturing Example 13-1-3 and this crude product (180 mg) was added triethylamine (125 µL, 0.900 mmol) at room temperature, which was stirred for 2 hours at room temperature. Water was added to the reaction solution at room temperature, which was extracted with ethyl acetate, The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = $2:1 \rightarrow 3:1$), and then further purified by reverse-phase high performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1% trifluoroacetic acid) to obtain the title compound (3.20 mg, 1.72%) as a ditrifluoroacetic acid salt. MS m/e(ESI) 392.19(MH+)

[Example 159] 3-(3-(4-(2-Pyridin-2-yl-ethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1358]

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[1359] To a mixture of (4-(2-pyridin-2-ył-ethyl)-phenyl)-acetohydroximoyl chloride hydrochloride (780 mg, 2.51 mmol) described in Manufacturing Example 93-1-8 and dimethylformanide (10 mL) yeare added 3-ethynyl-pyridin-2-6-diamine (86 mg, 0.721 mmol) described in Manufacturing Example 13-1-3 and triethylamine (10.5 mL, 7.53 mmol), which was stirred for 3 hours at room temperature. Water and ethyl acetate were added to the reaction mixture, and the organic layer was separated. This organic layer was vashed with water and saturated aqueous sodium floride and dried over anthydrous manuschium sufflex, and the solvent was evaporated under a reduced pressure. The residue was purified by

NH silica gel column chromatography (ethyl acetate : heptane = 4 : 6 then ethyl acetate) to obtain the title compound (80 mg,30%).

¹H-NMR Spectrum (CDCl₃) 6 (ppm); 3.00-3.10 (4H, m), 3.98 (2H, s), 4.46 (2H, brs), 5.25 (2H, brs), 5.91 (1 H, d, J = 8.4 Hz), 5.99 (1H, s), 7.07 (1 H, d, J = 8.0 Hz), 7.15 (2H, d, J = 8.0 Hz), 7.15 (2H, d, J = 8.0 Hz), 7.19 (2H, d, J = 8.0 Hz), 7.10 (2H, d, J = 8.0 Hz), 7.1

[Example 160] 3-(3-(1-(3-Fluoro-benzyl)-1 H-pyrrol-3-ylmethyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[1360]

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HA CANA

[1361] 1-(3-fluor-obenzy)-1/H-pyrrol-3-yl)-acetohydroximoyl chloride (1.1 g) was obtained according to the methods similar to those of Manufacturing Example 57-1-3, using 1-43-fluoro-benzy)-3-(2-nitro-ethy)-1/H-pyrrole (1.7 g, 6.9 mmol) described in Manufacturing Example 160-1-1. The title compound (4.7 mg, 4.3%) was obtained according to the methods similar to those of Example 12, using 3-ethynyl-pyridin-2,6-diamine (40 mg, 0.30 mmol) described in Manufacturing Example 13-1-3 and the above-mentioned 1-(3-fluoro-benzyl)-1/H-pyrrol-3-yl)-acetohydroximoyl chloride (400 mg, 1.5 mmol).

"I+NMR Spectrum (DNSO- d_0) δ (ppm): 3.7 (2H, s), 5.05 (2H, s), 5.77 (2H, brs), 5.83 (1 H, d, J = 8.0 Hz), 5.99 (1 H, dd, J = 2.0, 2 DHz), 5.09 (2H, brs), 6.53 (1 H, s), 6.72 (1 H, dd, J = 2.0, 2 DHz), 6.79 (1 H, dd, J = 2.0, 2 DHz), 6.97 (1 H, dd, J = 2.0, 2 DHz), 6.97 (1 H, dd, J = 2.0, 2 DHz), 6.97 (1 H, dd, J = 8.0 Hz), 7.067 (1 H, dd, J = 8.0 Hz), 7.067

[1362] The starting material, 1-(3-tituoro-benzyi)-3-(2-tituro-etnyi)-17-pytrole, was synthesized as folio

[Manufacturing Example 160-1-1] 1-(3-Fluoro-benzyl)-3-(2-nitro-ethyl)-1H-pyrrole

[1363]

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[1364] The title compound (1.7 g, 48%) was obtained according to the methods similar to those of Manufacturing Examples 57-1-1 to 57-1-2, using 1-(3-fluorobenzyl)-1 H-pyn-ole-3-carbaldehyde (2.9 g, 14 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.00 (2H, t, J = 6.8 Hz), 4.67 (2H, t, \dot{J} = 6.8 Hz), 5.05 (2H, s), 5.94 (1 H, dd, J = 2.0, 2.0 Hz), 6.88 (1 H, dd, J = 2.0, 2.0 Hz), 6.90-6.95 (1 H, m), 6.98 (1 H, d, J = 8.0 Hz), 7.08-7.12 (1 Hm), 7.33-7.49 (1 H, m).

[Example 161] 3-(3-(6-Phenylsulfanyl-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1365]

10 [1366] To a terrahydrofuran (4 mt.) solution of the (6-phenylsulfanyl-pyridin-3-yt)-sectohydroximoyl chloride (100 mg, 0.359 mmo) seached in Manufacturing Example (9.714 and 3.6 sthryel pyridin-2-6 diamine (15 mg, 0.13 mmo) described in Manufacturing Example 13-1-3 was added triethylamine (55 µL, 0.40 mmo), which was stirred under nitrogen atmosphere for 1 hour at 50°C. Water was added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over enhydrous magnesium surfact. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica get column chromatography (ethyl acetate: methanol = 10.1) to dobtin the title compound (26 mg, 65°M).

1H-NMR Spectrum (CDCl₂) δ (ppm):3.94 (2H, s), 4.51 (2H, s), 5.26 (2H, s), 5.92 (1 H, d, J = 8.4 Hz), 5.97 (1 H, s), 6.86 (1 H, d, J = 8.4 Hz), 7.37 (1 H, dd, J = 2.4, 8.2 Hz), 7.40-7.43 (3H, m), 7.46 (1 H, d, J = 8.2 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 7.57-7.60 (2H, m), 8.39 (1 H, d, J = 8.4 Hz), 8.39 (1 H, d, J = 8.4 Hz), 8.39 (1 H, d, J = 8.4 Hz), 8.39 (1 H, d, J = 8.

[Example 162] 3-(3-(4-(3-Methoxy-benzyloxy)-benzyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[1367]

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[1368] To a tetrahystroturan (3 mL) solution of 4-(6-(2-d-alienino-pyrition 3-yh-)isoxazcl-3-ymethyl)-phenol (30 mg, 0.11 mmol) described in Maunifacturing Example 18-11 was added a 5 No sodium hydroxide aqueus solution (21 z. µ., 0.11 mmol), which was dissolved by irradialing ultrasonic wave for 1 minute. The neaction solution was concentrated under a reduced pressure, which gave a white solid. To a mixture of this solid and N.N-dimethylformamide (1 mL) was added an N.N-dimethylformamide (1 mL) was added an N.N-dimethylformamide (1 mL) was added to 1-2 hours at 60°C. This reaction mixture was cooled to norn temperature, and then partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueus sodium chloride, dried over antyrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH elities ge column chloridorgraphy (ethyl societate) to obtain the title compound (344 mg, 81 %), J = 8.4 hz), 6.10 (2H, brs.), 6.34 (H, sh., 6.8-6.89 (H, mh., 6.85 (2H, sh., 6.87 (2H, m), 7.21 (2H, sh., 7.21 (2H, sh., 7.21 (2H, sh., 7.81 (2H, sh.,

[Example 163] 3-(3-(4-(6-Methoxy-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

7.29 (1 H, dd, J = 8.0, 8.4 Hz), 7.51 (1 H, d, J = 8.4 Hz).

[1369]

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[1370] To a tetrahydrofuran (3 m.l.) solution of 4-(5-(2-6 diamino pyridin-3-y)-isoxazol-3 ylmethyl)-phenol (30 mg. 0.11 mmol) described in Manufacturing Example 18-1-1 was added a 5 N sodium hydroxide aqueous solution (21.2 µL, 0.11 mmol), which was dissolved by irradiating ultrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white solid. To a mixture of this solid and N.N-dimethylformanide (1 mL) was added an N.N-dimethylformanide (1 mL) solution of 1-chloromethyl-emboxyyridine (20.0 mg. 0.13 mmoly described in Manufacturing Example 99-1-2, which was stirred for 1 hour at 80°C. This reaction mixture was cooled to room temperature, and then partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium cholinde, dired over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate) to obtain the title compound (26.1 m. 61%).

1-H-NMR Spectrum (DMSO-d₈) 6 (ppm): 3.85 (3H, s), 3.88 (2H, s), 5.06 (2H, s), 5.79 (2H, brs), 5.82 (1 H, d, J = 8.4 Hz), 6.11 (2H, brs), 6.34 (1 H, s), 8.75 (1 H, dd, J = 0.8, 8.4 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.05-7.08 (1 H, m), 7.20-7.24 (2H, m), 7.51 (1 H, d, J = 8.8 Hz), 7.69-7.74 (1 H, m).

Example 164] 3-(3-(6-(Pyridin-3-yloxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1371]

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[1372] To a mixture of 5-(2-nitro-ethyl)-2-(pyridin-3-yloxy)pyridine (157.0 mg, 0.64 mmol) described in Manufacturing Example 100-1-2 and methanol (6 mL) was added lithium methoxide (48.7 mg, 1,28 mmol) at room temperature, which was stirred for 1 hour. The reaction mixture was then concentrated under a reduced pressure, which gave a white solid. To a mixture of this solid in dichloromethane (4 mL) and tetrahydrofuran (2 mL) was added titanium tetrachloride (155.0 μL, 1.41 mmol) under nitrogen atmosphere at -78°C, which was stirred for 3 hours at 0°C. Water was added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under a reduced pressure. To a mixture of the resulting residue (30.7 mg), 3-ethynyl-pyridin-2,6-diamine (15.4 mg, 0.12 mmol) described in Manufacturing Example 13-1-3, tetrahydrofuran (1 mL), and dimethyl sulfoxide (1 mL) was added triethylamine (32.4 µL, 0.23 mmol) at room temperature, which was stirred for 1 hour at 55°C. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure. The residue thus obtained was purified by reversephase high performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trifluoroacetic acid), and then further purified by preparative thin-layer chromatography (NH silica gel, ethyl acetate) to obtain the title compound (3.6 mg, 9%).

1H-NMR Spectrum (CDCL₃) 6 (ppm): 3.98 (2H, s), 4.52 (2H, brs), 5.28 (2H, brs), 5.93 (1 H, d, J = 8.4 Hz), 6.01 (1 H, s), 6.95 (1 H, dd, J = 0.4, 8.4 Hz), 7.34 (1 H, ddd, J = 0.8, 4.4, 8.4 Hz), 7.50-7.53 (1H, m), 7.66 (1H, dd, 2.4, 8.4 Hz), 8.10 (1H, dd, J = 0.8, 2.4 Hz), 8.45 (1 H, dd, J = 1.2, 1.6, 4.8, 5.2 Hz), 8.50 (1 H, d, J = 2.8 Hz).

MS m/e (ESI) 361.05(MH)

[Example 165] 6-Methoxymethyl-3-(3-(4-(5-methyl-furan-2-ylmethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1373]

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[1374] To a mixture of (4-(5-methyl-furan-2-y/methyl)-phenyl)-acetohydroximoyl chloride (11 mg, 0.043 mmoi) described in Manufacturing Example 46-1-6 and tetrahydrofuran (1 mL) were added 3-ethynyl-6-methoxymethyl-pyridin-2-y/methyl (6.5 mg, 0.035 mmoi) described in Manufacturing Example 26-1-7 and triethylamine (8.6 mL), 0.058 mmoi), which was stirred for 3 hours at 40°C. The reaction mixture was allowed to room temperature, water was added at the same temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromotography (ethyl acetate: heptane = 2: 3) to obtain the title compound (9.2 mg, 58%, purity, 84%) as a mixture with the starting material 3-ethyl-6-methoxymethyl-pyridin-2-ylaminou.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.24 (3H, s), 3.46 (3H, s), 3.90 (2H, s), 4.02 (2H, s), 4.42(2H, s), 5.46 (2H, brs), 5.85-5.87 (2H, m), 6.23 (1 H, s), 6.81 (1 H, d, J = 7.9 Hz), 7.21 (4H, s), 7.71 (1 H, d, J = 7.9 Hz).

25 [Example 1661 6-Methoxymethyl-3-(3=(4-(pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine.

[1375]

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[1376] To a methanol (1.5 mL) solution of 4-(5-(2-amino-6-methoxymethyl-pyridin-3-yf)isoxazol-3-yfmethyl)-phenol (60 mg, 0.16 mmol) described in Manufacturing Example 166-11 was added a 1 N sodium hydroxide aqueous solution (160 µL, 0.16 mmol), which was concentrated under a reduced pressure. Nl-4-dimethyl promamile (1.5 mL) was added to the residue thus obtained at room temperature, and 2-plooly chloride (29 mg, 0.23 mmol; this 2-plooly) chloride was prepared by adding a 5 N sodium hydroxide aqueous solution to 2-plooly chloride hydroxidoride) was added to the reaction mixture at the same temperature. The reaction mixture was stirred for 100 minutes at the same temperature. Water was added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 4 : 1) to obtain the title compound (32 mg, 52%). H-NMR Spectrum (DCCL) & Gipm. 3 ad (6H, s), as 9 (2H, s), as 20 (H, s), s, 52 (2H, s), s, 52 (3H, s)

[1377] The starting material, 4-(5-(2-amino-6-methoxymethyl-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol, was synthesized as follows.

[Manufacturing Example 166-1-1] 4-(5-(2-Amino-6-methoxymethy(-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol

55 [1378]

2 [1379] To a mixture of 3-(3-(4-benzy)cay-benzy)-isorazeol-5-y)-6-methoxymethylpyridin-2-ylamine (30 mg, 0.075 mmol) described in Example 26 and dichloromethane (1 mL) was added boron tribromide (220 µL, 1 M dichloromethane solution, 0.22 mmol) at 7-8°C, which was stirred for 1 hour at 0°C. The reaction mixture was coded to 7-8°C, methand was added that the same temperature, and the excess boron tribromide was quenched. The reaction mixture was gradually allowed to room temperature, as dodlum acetate aqueous solution mas added to the reaction mixture at room temperature, 6 which was neutralized, after which water was added, and the mixture was extracted with ethyl acotate. The organic layer was washed with saturated aqueous sodium choride, and was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : heptane = 2 : 1) to obtain the title compound (4.6 mg, 20%).

¹H-NMR Spectrum (CDCl₂) δ (ppm): 3.47 (3H, s), 3.98 (2H, s), 4.43 (2H, s), 5.50 (2H, br s), 6:22 (1 H, s), 6.78-6.83 (3H, m), 7.13-7.16 (2H, m), 7.73 (1 H, d, J = 7.9 Hz)

[Example 167] 6-Methoxymethyl-3-(3-(6-phenoxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1380]

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[1381] To a tetrahydrofuran (2 mL) solution of (2-phenoxy-pyridin-5-y)-acetohydroximoyl chlorida (93 mg, 0.36 mmol) described in Manufacturing Example 40-14 and 3-ethnynl-6-methoxymethyl-pyridin-2-ylamine (32 mg, 0.20 mmol) described in Manufacturing Example 26-1-7 was added triethylamine (55 µL, 0.39 mmol), which was stirred under nitrogen atmosphere for 5 hours and 26 minutes at 50°C. Water was added to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueues sodium chlorida, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by slifca gel column chromatography (heptane: ethyl acetate = 1: 1) to obtain the title compound (54 mg, 71 %).

¹H-NMR Spectrum (DMSO-d_e) 8 (ppm):3.35 (3H, s), 4.03 (2H, s), 4.33 (2H, s), 6.31 (2H, s), 6.73 (1 H, d, J = 7.7 Hz), 6.83 (1 H, s), 7.00 (1 H, d, J = 8.4 Hz), 7.10-7.12 (2H, m), 7.18-7.22 (1 H, m), 7.38-7.44 (2H, m), 7.81 (1 H, dd, J = 2.4, 8.4 Hz), 7.89 (1 H, d, J = 7.9 Hz), 8.16 (1 H, d, J = 2.4 Hz).

[Example 168] 3-(3-(4-(5-Chloro-furan-2-ylmethyl)-benzyl)-isoxazol-5-yl)-6-methoxymethyl-pyridin-2-ylamine

[1382]

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ON NH.

[1883] To a mixture of (4-(5-chloro-furan-2-yinethyl)-phenyl)-actohydroxinoy), chloride (25 mg, 0.088 mmol) described in Manufacturing Example 82-16 and tetralydroturan (1 ml.) were added 3-chlywf-6-methoxymethy-pridin-2-ylemine (11 mg, 0.089 mmol) described in Manufacturing Example 26-17 and triethylamine (19 µL, 0.014 mmol), which was atimed for 1 hour at 50°C. The reaction mixture was allowed to room temperature, water was added at the same temperature, and the mixture was extracted with ethyl acetale. The organic layer was washed with saturated acqueous sodium chloride, and was concentrated under a reduced pressure. The residue thus obtained was purified by reverse-phase high performance fluid chromatography (using an acetorhinile-water mobile phase containing 0.1 % utiliurocaecis acid) to obtain the title compound 5x a crude product. This product was then purified by NH silica gel column chromatography (ethyl acetate: heptane = 1; 1) to obtain the title compound (75 mg, 27°%).

MS m/e(ESI) 410.10(MH)

"H-MMR Sporting (CDC)₃ is (5ppm): 3.46 (3H, s), 3.90 (2H, s), 4.93 (2H, s), 4.42 (2H, s), 5.46 (2H, br s), 5.98-5.99 (1 H, m), 6.04-6.05 (1 H, m), 6.24 (1 H, s), 6.81 (1 H, d, J = 7.9 Hz), 7.20 (2H, d, J = 8.1 Hz), 7.23 (2H, d, J = 8.1 Hz), 7.72 (1 H, d, J = 7.9 Hz),

[Example 169] (6-Amino-5-(3-(4-benzyloxy-benzyl)-isoxazol-5-yl)-methanol

[1384]

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[1385] To a mixture of 4-benzyloxy-phenyl-acetohydroximoyl chloride (9.8 mg., 0.043 mmol) described in Manufacturing Example 1-13 and tetahydrotura (it ml.) were added (6-amino-5-ethyry-byridin-2-yl-phenbane) (6.1 mg., 0.024 mmol, purity: 57%) described in Manufacturing Example 169-1-2 and triethylamine (6.5 µL, 0.047 mmol), which was stirred for 1 hour at 50°C. The reaction mixture was allowed to room temperature, water was added at the same temperature, and tem mixture was extracted with eithyl acetate. The organic layer was weathed with settraded equeue secling michoride, and was concentrated under a reduced pressure. The residue thus obtained was purified by reverse-phase high performance [iquid chromatography (singt an acetoinified-water mobile phese containing 0.1 st influoracedic acid) to obtain the title compound as a crude product. This product was then purified by NH silica gel column chromatography (ethyl acetate) to obtain the title compound (3.3 mg., 36%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 4.00 (2H, s), 4.63 (2H, s), 5.05 (2H, s), 5.52 (2H, brs), 6.22 (1 H, s), 6.63 (1 H, d, J = 7.9 Hz), 6.93-6.97 (2H, m), 7.19-7.22 (2H, m), 7.30-7.44 (5H, m), 7.70 (1 H, d, J = 7.9 Hz).

[1386] The starting material, (6-amino-5-ethynyl-pyridin-2-yl)-methanol, was synthesized as follows.

[Manufacturing Example 169-1-1] 2-Amino-6-hydroxymethyl-pyridine-3-carbaldehyde

[1387]

MS m/e(ESI) 388.01 (MH+)

[1388] To a mixture of 2-amino-6-methoxymethyl-pyridine-3-carbaldehyde (57 mg, 0.34 mmol) described in Manufacturing Example 26-1-6 and dichloromethane (2 mt), was added boron tribromide (1.0 mt, 1 M dichloromethane solution, 1.0 mmol) at -78°C, which was stirred for 1 hour at 0°C. The reaction mixture was cooled to -78°C, methanol was added at the same temperature, and the excess reagent was quenched. The reaction mixture was gradually allowed

to room temperature and was neutralized by adding an ammonium aqueous solution (28%). Whete was added to the reaction mixture, which was extracted with ethyl sectets. The organic layer was washed with saturated aqueous sodium chlorido, and was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetter 5 rectane = 4:11 to obtain the title compound 16 ma. 34%).

5 1H-NMR Spectrum (DMSO-d₀) δ (ppm): 4.40 (2H, d, J = 5.9 Hz), 5.42 (1 H, t, J = 5.9 Hz), 6.86 (1 H, d, J = 7.7 Hz), 7.52 (2H, br s), 8.00 (1 H, d, J = 7.9 Hz), 9.81 (1 H, s).

[Manufacturing Example 169-1-2] (6-Amino-5-ethynyl-pyridin-2-yl)-methanol

0 [1389]

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20 [190] To a mixture of 2-emino-6-hydroxymethyl-pyridino-3-carbaldehyte (16 mg, 0.11 mmol) described in Manufacturing Exemple 169-1-1 and methanol (1.5 m.) were added dimethyl (1-45az-2-boxoppyyl)hosphomate (30 mg, 0.16 mmol) and potassium carbonate (23 mg, 0.17 mmol) at -10°C, which was stirred for 10 minutes at 0°C, and then for another 6 hours at room temperature. A saturated ammonium chloride aqueous soldium and saturated aqueous sodium conformation of the respective of the same temperature, which was extracted with ethyl sociate. The organic sigverwas weaked with saturated aqueous sodium chloride, and was concentrated under anduced pressure. The residue thus obtained was purified by silica gel column chromatography (ethyl acetate) to obtain the title compound (13 mg, 47%, curifier, 57%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 3.41 (1H, s), 4.60 (2H, s), 5.12 (2H, br s), 6.56 (1 H, d, J = 7.5 Hz), 7.56 (1 H, d, J = 7.7 Hz).

[Example 170] 3-(3-(4-benzyloxy-benzyl)-isoxazol-5-yl)-6-methyl-pyridin-2-ylamine

[1391]

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[1382] To a tetrahydrofuran (2 mL) solution of 4-benzy/oxy-phenyl-excelohydroximoyl chloride (68 mg, 0.23 mmo) described in Munufacturing Example 1-1-3 and 3-drynyl-6-methyl-gyldin-2ylamine (20 mg, 0.15 mmo)) described in Manufacturing Example 170-1-5 was added triethylamine (42 µL, 0.30 mmo) at room temperature, which was stirred for 4 hours at 50°C. Water was added to the reaction mixture, which was extracted with ethyl acetate. The organic lovel, died over an hydrosu magnesium sulfate, and filtered, and the filtrate was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (legistre et et 91), and then further purified by reverse phase high performance liquid chromatography (lusing an aceton/trile-water mobile phase containing 0.1 % trifluoreacetic acidy) to obtain the title compound (26 mg, 34%) as a trifluoroacetic acidy).

MS m/e (ESI) (MH+) 372.23(MH+)

[1393] The starting material; 3-ethynyl-6-methyl-pyridin-2-ylamine, was synthesized as follows.

55 [Manufacturing Example 170-1-1] 2-Amino-6-chloro-nicotinic acid ethyl ester

[1394]

[1395] To ethanol (20 mL) were added concentrated sulfuric acid (10 mL) and 2-amino-6-chloro-nicotinic acid (6.3 g, 27 mmol, purity, 75%) described in Manufacturing Example 26-1-1 on an ice bath, which was stirred overnight at 65°C. The reaction mixture was gradually cooled, after which a sodium hydrogencarbonate aqueous solution was added to neutralize the mixture. The precipitated solids were filtered to obtain the title compound (4.1 g, 74%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.38 (3H, t, J = 7.1 Hz), 4.34 (2H, q, J = 7.1 Hz), 6.62 (1 H, d, J = 8.1 Hz), 8.07 (1H, d, J = 8.1 Hz).

[Manufacturing Example 170-1-2] 2-Amino-6-methyl-nicotinic acid ethyl ester

[1396]

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[1397] To a N-methylogyroldinone (20 mL) solution of 2-amino-6-chloro-nicotinic acid ethyl ester (2.00 g, 7.78 mmol) described in Manufacturing Example 170-1-1 were added tetramethylifin (1.62 mL, 1.7 mmol) and tetrakis(riphenyl-phosphine)palladium(0) (839 mg, 0.778 mmol), which was stirred under nitrogen atmosphere for 5 hours and 40 minutes at 130°C. Water was added to the reaction mixture at room temperature, which was extracted with ethyl acottats. The organic layer was washed with water and saturated aqueous sodium chloride, died over anthydrous magnesium sulfact, and filtered, and the filtrate was concentrated under a reduced pressure. The residue thus obtained was purified by NH elidica gel column chromatography (heptane: ethyl acottate = 2.1) and then further purified by silica gel column chromatography (heptane: ethyl acottate = 2.1) to obtain the title compound (670 mg, 48%).

[Manufacturing Example 170-1-3] (2-Amino-6-methyl-pyridin-3-yl)-methanol

[1398]

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Hz), 8.03 (1 H, d, J = 8.0 Hz).

[1399] To a tetrahydrofuran (12 m.l.) solution of lithium aluminum hydride (706 mg, 14.9 mmol, putily, 80%), was added 2-amin o-6-methyl-incitnic acid ethyl ester (670 mg, 3.72 mmol) described in Manufacturing Example 170-12 at 0°C, which was stirred for 30 minutes at room temperature. Water (706 µ.l.), a 5 N sodium hydroxide aqueous solution (706 µ.l.), and water (2.12 m.l.) were added to the reaction mixture in that order at 0°C, which was filtered through a Cellite pad. The filtrate was concentrated under a reduced pressure, and the residue was purified by HI silica gel column chromatography (lefty) acetate: methanol = 10:1) to obtain the title compound (879 mg, 74%).

¹H-NMR Spectrum (CDCl₂) δ (ppm):2.38(3H, s), 4.61 (2H, s), 5.08 (2H, s), 6.48 (1H, d, J=7.2Hz), 7.23 (1H, d, J=7.2Hz).

[Manufacturing Example 170-1-4] 2-Amino-6-methyl-pyridine-3-carbaldehyde

[1400]

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[1401] To a methylene chloride (8 ml.) solution of (2-amino-9-methyl-pyridin-3-yl-)-methanol (379 mg. 2.74 mno.) described in Manufacturing Exemple 170-1-3 was added manganese (IV) dioxide (1.19 mg. 13.7 mmol) at room temperature, which was stirred for 11 hours at room temperature. The reaction mixture was filtered through a Cellite pad, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl ceated = 1.2 to obtain the title compound (328 mg. 88%).

¹H-NMR Spectrum (CDCl₂) δ (ppm):2.44 (3H, s), 6.61 (1 H, d, J = 7.9 Hz), 7.69 (1 H, d, J = 7.9 Hz), 9.80(1 H, s).

[Manufacturing Example 170-1-5] 3-Ethynyl-6-methyl-pyridin-2-ylamine

[1402]

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[1403] To a tetrahydrotruran (5 m.l.) solution of discopropylamine (439 µ.l., 3.13 mmol) was added n-butyl lithium (1,81 h., 1.8 h. hexace solution, 2.89 mmol) under nitrogen atmosphere at .75°C, which was stirred for 15 minutes at .0°C. Then, trimethylsily/disconethane (1,81 m.l., 2.1 tetrahydrotruran solution, 3.62 mmol) was added to the reaction mixture at .78°C, which was stirred for 50 minutes at .78°C to the reaction mixture was added at eterthyldrotrural (P.M.) solution of 2-amino-8-methyl-pyridine-3-carbaldehyde (328 mg, 2.41 mmol) described in Manufacturing Example 170-14 at .78°c, which was stirred for 26 minutes at .78°C, which was stirred for 26 minutes at .78°C, which was stirred for 26 minutes at .78°C, and the temperature was slowly raised, after which water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, died over anthyrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced prosseure. The residue was purified by NH silice gel column chromatography (heptane: ethyl acetate = 2:1) to obtain the title compound (243 mg, 78%).

¹H-NMR Spectrum (CDCl₃) δ (ppm):2.39 (3H, s), 3.38 (1 H, s), 5.07 (2H, s), 6.49. (1 H, d, J=7.7 Hz), 7.47 (1 H, d, J=7.7 Hz).

[Example 171] 6-Methyl-3-(3-(4-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin 2-ylamine

[1404]

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NH, NH,

[1405] To a tetrahydrofuran (2 mL) solution of 3-ethynyl-5-methyl-pyridin-2-ylamine (20 mg, 0.15 mmol) described in Manufacturing Example 170-15 were added 4-(pyridin-2-ylamine)-phenyl-acetohydraximyl chlorido (3 mg, 0.23 mmol) described in Manufacturing Example 2-1-5 and triethylamine (42 μ L, 0.30 mmol) at room temperature, which was stirred for 2 hours and 50 minuties at 50°C. Water was added to the reaction mixture at room temperature, which was extracted with particle acetae; the roganic leyer was washed with saturated aqueous sodium-chloride, directore arrhydrous magnesium sulfate, and filtered, after which the filtrate was concentrated under a reduced pressure. The residue was purified by NH sits age glo column chromatography floration: ethylamic ethyl acetae 2-11), and then further purified by reverse-phase high performance liquid chromatography (using an acetoritrile-water mobile) phase containing 0.1 % trifluoroacetic acid) to obtain the title compound 62 mg, 32%) as a trifluoroacetic acid salt.

MS m/e (ESI) (MH+) 373.19(MH+)

14-NMR Spectrum (DMSO-d_d) δ (ppm):2.28 (3H, s), 4.00 (2H, s), 5.30 (2H, s), 6.17 (2H, s), 6.54 (1 H, d, J = 7.9 Hz), 6.72 (1 H, s), 6.83 (1 H, d, J = 8.4 Hz), 7.89 (2H, d, J = 8.2 Hz), 7.67-7.72 (1H, m), 7.75 (1H, d, J = 7.9 Hz), 8.14-8.15 (1 H, m).

Example 172] 5-chloro-3-(3-(4-pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1406]

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[1407] To a mixture of 3-(3-(4-benzyloxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine (10.0 mg, 0.03 mmol) described in Example 2 and N.N-dimethylformamide (1 mL) was added N-chlorosuccinimide (3.7 mg, 0.03 mmol), which was stirred for 2 hours at room temperature. This mixture was then stirred for 1 hour at 50°C, and then for another 14 hours at room temperature. Water was added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over analydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue thus obtained was purified by reversephase high performance (figuid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trifluoroacetic acid to obtain the title compound (4.0 mg, 11 %) as a diriffitronescetic acid salt.

14-NMR Spectrum (CD₀CD) δ (ppm) :4.08 (2H, s), 5.34 (2H, s), 6.69 (1 H, s), 6.83 (1 H, d, J = 8.4 Hz), 6.99-7.02 (1 H, m), 7.33 (2H, d, J = 8.0 Hz), 7.42 (2H, d, J = 8.0 Hz), 7.75-7.79 (1 H, m), 7.96 (1 H, d, J = 2.4 Hz), 8.04 (1 H, d, J = 2.8 Hz), 8.12-8.17 (1 H, m).

MS m/e (ESI) 393.03(MH+)

[Example 173] 3-(3-(4-Benzyloxy-benzyl)-isoxazol-5-yl)-5-fluoro-pyridin-2-ylamine

[1408]

[1409] To a tetrahydrotruna (10 mL) mixture of 3-ethynyl-5-fluoro-pyridin-2-ylamine (128 mg, 0.85 mmol) described in Manufacturing Example 173-1-2 and 4-benzylosy-phenyl-acetohydroximoyl chloride (314 mg, 1.14 mmol) described in Manufacturing Example 1-13 was added triethylamine (284 µL, 1.90 mmol) at room temperature, which was stirred for 1 hour at 56°C, and then for another hour at 60°C. This reaction mixture was cooled to room temperature, and then partitioned into eithyl acetale end water. The organic layer was separated, washed with water and saturated aqueous

sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue thus obtained was purified by NH silica gel column chromatography (heptane: ethyl acetate = 3:11 to obtain the title compound (212 m. 60%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.97 (2H, s), 5.08 (2H, s), 6.24 (2H, brs), 6.90 (1 H, s), 6.98 (2H, d, J = 8.0 Hz), 7.24 (2H, d, J = 8.8 Hz), 7.28-7.45 (5H, m), 7.83-7.90 (1 H, m), 8.10-8.12 (1 H, m).

[1410] The starting material, 3-ethynyl-5-fluoro-pyridin-2-ylamine, was synthesized as follows.

[Manufacturing Example 173-1-1] 5-Fluoro-3-iodo-pyridin-2-ylamine

[1411]

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[1412] To a mixture of 2-emino-5-fluorophydine (2.0 g, 17.8 mmol) and dimethy sulfoxide (50 mL) was added Niodosuccinimide (4.8 g, 21.4 mmol), which was stirred for 1 hour at room temperature. A suitable amount of acetic acid was added to this mixture, which was stirred for 1 hour at the same temperature, and then stirred for another 3 hours at 55°C. This reaction mixture was cooled to room temperature, after which a saturated sodium hydrogencarbonate aqueous solution was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chioride, dried over anhydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue thus obtained was purified by NH silica gel column chrometography (ethyl acetate) to botain the title comound (75°Im or 18%).

¹H- NMR Spectrum (DMSO-d_B) δ (ppm): 5.99 (2H, brs), 8.05 (1H, dt, J = 2.8, 8.0 Hz), 8.80-8.81 (1H, m).

[Manufacturing Example 173-1-2] 3-Ethynyl-5-fluoro-pyridin-2-ylamine

[1413]

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FUN NH,

40 [1414] To a mixture of 5-fluoro-3-loido-pyridin-2-ylamine (751 mg. 3.16 mmol) described in Manufacturing Example 173-11. Immitsylallyiacelyiace (872 mg. 3.8 mmol), no.9-cell (1004) (80.2 mg. 3.2 mmol), N3-cell (1005) (183 mg. 0.16 mmol), which was stirred for 3 hours under nitrogen almosphere at 70°C This reaction solution was cooled to room temperature, and then partitioned into ethyl acetate and water. The organic layer was separated, whether With water 45 and seturated acqueous sodium chloride, dried over enhydrous magnesium sulfate, and filbrerd. The fiftrate was concentrated under a reduced pressure, and the residue thus obtained was purified by N1 silica gel column chromatography and then silica gel column chromatography (heptane: ethyl acetate = 1: 1) to obtain the title compound (123 mg. 30%). H1-NMR Spectrum (DMS-O-4, j Epm) 4.5 cell (14, j.d. 3.2 L/H), 7.5 fcl (14, j.d. 3.2, 8.8 Hz), 7.7 fcl, 14, j.d. 3.2 L/H.

[Example 174] 5-Fluoro-3-(3-(4-(5-fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1415]

1416] To 4-15-(2-amino-5-fluoro-pyridin-3-yh-isoxazol-3-yhnethyl)-phenol (20.0 mg, 0.07 mmol) described in Manufacturing Example 174-1-1 were added tetrahydrofuran (3 mL) and a 5 N sodium hydroxide aqueous solution (14.0 μL, 0.07 mmol), which was dissolved by irradiating ultrasonic wave for 1 minute. Next, the reaction solution was concentrated under a reduced pressure, which gave a white solid. To a mixture of this solid and N N-dimethyformamide (1 mL) solid nor 6 2-chirorembty-5-fluoro-pyridine (11.2 mg, 0.08 mmol) described in manufacturing Example 41-1-2, which was stirred for 1 hour at 60°C. The reaction mixture was cooled to room temperature and then partitioned into water and ethyl accelate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over analydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane : ethyl acetate = 1 : 1) to 0 dain the title compound (2-4 mc. 89%).

²⁹ 1H-NMR Spectrum (DMSO-d_b) 5 (ppm):3.98 (2H, s), 5.16 (2H, s), 6.25 (2H, brs), 6.91 (1 H, s), 7.00 (2H, d, J = 8.8 Hz), 7.26 (2H, d, J = 8.4 Hz), 7.577.63 (1 H, m), 7.77 (1 H, dt, J = 2.8, 8.8 Hz), 7.87 (1 H, dd, J = 2.8, 9.2 Hz), 8.12 (1 H, d, J = 3.2 Hz), 8.12 (1 H, d), 3.2 Hz), 8.13 (1 H, d), 3.3 (1 Hz), 8.56 (1 H, d), 3.3 (1 Hz), 6.15 (1 H, d), 7.56 (1 H, d), 7.57 (1 H, d), 7.77 (

[1417] The starting material, 4-(5-(2-amino-5-fluoro-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol, was synthesized as follows

[Manufacturing Example 174-1-1] 4-(5-(2-Amino-5-fluoro-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol

[1418]

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F () N

40 [1419] To a (180 mg, 0.44

[1419] To a trifluoroaccitic acid (5 mL) solution of 3-(3-(4-benzyloxy-benzyl)-slowazed-5-yl)-5-fluor-pyridin-2-ylamine (180 mg. 0.48 mmo) described in Example 173 was added thiolande (225 js. 1, 193 mmo), which was strend for 6 hours at room temperature. A saturated sodium hydrogencarbonate aqueous solution was added to this reaction solution at 0°C, which was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated acueous sodium inchoride, circle over anhydrous mangeatum satilate, and filtered. The filter was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ethyl acetate 1=12-ethyl acetate) to obtain the title compound (13-4.0 mg. 98%).

 $^{1}\text{H-NMR Spectrum (DMSO-d}_{6}) \, \delta \, (\text{ppm}) : 3.91 \, (2\text{H}, \, \text{s}), \, 6.24 \, (2\text{H}, \, \text{brs}), \, 6.71 \, (2\text{H}, \, \text{d}, \, \text{J} = 8.8 \, \text{Hz}), \, 6.87 \, (1 \, \text{H}, \, \text{s}), \, 7.10 \, (2\text{H}, \, \text{d}, \, \text{J} = 8.8 \, \text{Hz}), \, 7.86 \, (1 \, \text{H}, \, \text{dd}, \, \text{J} = 2.8, \, 9.2 \, \text{Hz}), \, 8.11 \, (1\text{H}, \, \text{d}, \, \text{J} = 2.8 \, \text{Hz}), \, 9.32 \, (1 \, \text{H}, \, \text{brs}).$

[Example 175] 3-(3-(4-(4-Chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-5-fluoropyridin-2-ylamine

[1420]

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- 1421] Tetrahydrofuran (3 ml) and a 5 N sodium hydroxide aqueous solution (14 0 μL, 0.07 mmo) were acided to 4-(5 (2 amino 5 fluoro pyndin-3 yl)-isoxazoi-3 yimethyl) phenol (20.0 mg, 0.07 mmo) described in Manufacturing Example 174-1-1, which was dissolved by irradiating ultrasonic wave for 1 minute. Next, the reaction solution was concentrated under a reduced pressure, which gave a white solid. To a mixture of this solid and N,N-dimethylformamide (1 mL) was acided an N,N-dimethylformamide (1 mL) was acided an N,N-dimethylformamide (1 mL) described in manufacturing Example 51-1-2, which was stirred for 1 hour at 60°C. The reaction mixture was cooled to room temperature and then partitioned into water and ethyl acetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, died over anhydrous magnesium suitte, and filtered. The filtrate was concentrated under areduced pressure, and the residue was purified by NH silica gel column chromatography (heptane : ethyl scelate = 1 : 1) to bolish the tille compound (4.24 mg, a8/M).
- 1H-NMR Spectrum (DMSO-d₆) & (ppm): 3.98 (2H, s), 5.18 (2H, s), 6.24 (2H, brs), 6.90 (1 H, s), 7.01 (2H, d, J = 7.2 Hz), 7.26 (2H, d, J = 7.6 Hz), 7.50-7.54 (1 H, m), 7.60-7.64 (1 H, m), 7.85-7.89 (1H, m), 8.11-8.13 (1H, m), 8.55-8.57 (1 H, m), 7.60-7.64 (1 H, m), 7.60-7.64 (1 H, m), 7.60-7.69 (1H, m), 8.11-8.13 (1H, m), 8.55-8.57 (1 H, m),

[Example 176] 5-(3-(4-(Pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

25 [1422]

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[1423] To a tetralydrofuran (2.0 m), solution of 5-ethynyl-pyridin-2-ylamine (300 mg, 2.54 mmol) described in Manuffacturing Example 28-1-3 were added 4-(pyridin-2-yloxymathyl)-phenyl-acetohydroximoyl-chloride (1.05 g, 3.81 mmol) described in Manufacturing Example 2-1-5 and triethylamine (666 µL, 4.06 mmol), which was strired for 2 hours and 40 minutes at 50°C. Water was added to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, died over antipyrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate), and further purified by NH silica gel column chromatography (ethyl acetate): methanol = 10 : 1) to data the title compound (196 mg, 22%).

1H-NMR Spectrum (DMSO-d_b) δ (ppm):3.96 (2H, s), 6.30 (2H, s), 6.47 (1H, dd, J = 0.73, 8.6 Hz), 6.50 (2H, s), 6.55 (1 45 H, s), 6.83 (1 H, d, J = 8.2 Hz), 6.956-6.98 (1 H, m), 7.28 (2H, d, J = 8.1 Hz), 7.38 (2H, d, J = 8.1 Hz), 7.67-7.74 (2H, m), 8.148-16 (1 H, m), 8.86 (1 H, d, J = 2.4 Hz), 7.86 (2H, d, J = 8.1 Hz), 7.87 (2H, m), 8.148-16 (1 H, m), 8.86 (1 H, d, J = 2.4 Hz), 7.87 (2H, m), 8.148-16 (1 H, m), 8.86 (1 H, d, J = 2.4 Hz), 7.88 (2H, d, J = 8.1 Hz), 7.87 (2H, m), 8.148-16 (1 H, m), 8.86 (1 H, d, J = 2.4 Hz), 7.88 (2H, d, J = 8.1 Hz), 7.87 (2H, m), 8.148-16 (1 H, m), 8.86 (1 H, d, J = 2.4 Hz), 7.88 (2H, d, J = 8.1 Hz), 7.87 (2H, m), 8.148-16 (1 H, m), 8.86 (1 H, d, J = 2.4 Hz), 7.88 (2H, d, J = 8.1 Hz), 7.87 (2H, m), 8.148-16 (1 H, m), 8.98 (1 H, d, J = 2.4 Hz), 7.88 (2H, d, J = 8.1 Hz), 7.88 (2H, d, J = 8.1 Hz), 7.87 (2H, m), 8.148-16 (1 H, m), 8.98 (1 H, d, J = 2.4 Hz), 7.88 (2H, d, J = 8.1 Hz), 7.88 (2H, d, J = 8.1 Hz), 7.88 (2H, d, J = 8.1 Hz), 7.87 (2H, m), 8.148-16 (2H, d, J = 8.1 Hz), 7.88 (2H, d, J

[Example 177] 5-(3-(4-(Pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

50 [1424]

[1425] To a tetrahydrofuran (S.ml.) and acetone (S.ml.) solution of 4-(5-(6-aminopyridin-3-y)-isoxazoi-3-yimethy)-phenol (150 mg, 0.61 mmol) described in Manufacturing Example 17-1-1 was added a 6 N sodium Mydraxide aqueous solution (112 µL, 0.561 mmol), which was dissolved by irradiating ultrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a light-brown sodium salt (162 mg, quant.). A tetrahydrofuran solution of 2-picoly ichinoide (prepared by adding a 6 N sodium hydroxide aqueous sotiution (13 µL, 62 mmol to a solution of 2-picoly ichinoide hydrochloride (10 mg, 62 µmol) in tetrahydrofuran (1 ml.) and saturated aqueous sodium chloride (1 ml.) sitring for 1 minute, and then separarially the tetrahydrofuran layer) was added to a dimethyl sulfacide (2 ml.) solution of sodium salt (15 mg, 52 µmol) obtained above, which was streed for 30 minutes at 65°C. Water was added to the reaction mixture at room temperature, which was extracted with ethyl scetate. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: methanol = 20.1 to botain the title compound (4 mp, 24%).

"H-NMR Spectrum (CDCl₅) δ (ppm):3.97 (2H, s), 4.84 (2H, s), 5.20 (2H, s), 6.13 (1H, s), 6.55 (1 H, dd, J = 0.75, 8.6 Hz), 6.344.97 (2H, m), 7.197.24 (3H, m), 7.52 (1 H, d, J = 7.9 Hz), 7.71 (1 H, dt, J = 1.8, 7.7 Hz), 7.78 (1 H, dd, J = 2.4, 8.6 Hz), 8.84 (1H, dd, J = 7.2, 2.4 Hz), 8.95.86 (1 H, m).

25 [1426] The starting material, 4-(5-(6-amino-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol, was synthesized as follows.

[Manufacturing Example 177-1-1] 4-(5-(6-Amino-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol

[1427]

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40 [1428] To a trifluoroacetic acid (6 ml.) solution of 6-(3-44-benzyloxy-benzyl-isoxazo-6-yi)-pyridin-2-ylamine (270 mg, 0.755 mmo) described in Example 28 was added tibaniselos (858 mj. 3.02 mmo) at 0°C, which was strired to 1 thour and 20 minutes at room temperature. Sodium hydrogencarbonate and water were added to the reaction mixture at 0°C, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrour smagnesium sufface, and filtered. The filtrate was concentrated under a reduced pressure, 45 and the residue was purified by silica gel column chromatography (ethyl sociate: methanol = 10:1) to obtain the title compound (160 mg, 74%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm):3.84 (2H, s), 6.51 (1 H, d, J = 8.8 Hz), 6.53 (1 H, s), 6.57 (2H, s), 6.70 (2H, d, J = 8.4 Hz), 7.08 (2H, d, J = 8.4 Hz), 7.76 (1H, dd, J = 2.4, 8.8 Hz), 8.37 (1 H, d, J = 2.4 Hz), 9.28 (1 H, s).

Example 178] 5-(3-(4-(5-Methyl-furan-2-ylmethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1429]

[1430] To a mixture of (4-(6-methyf-turan-2-ymethyf)-phenyly-acetohydroximoyl chloride (38m.g. 0.14 mmol) described in Manufacturing Example 46-1-6 and tetrahydrotinan (1 ml.) were added 5-ethyrly-pydina-2-ylamne (15 mg. 0.13 mmol) described in Manufacturing Example 28-1-3 and treithylamine (35 ml., 0.25 mmol), which was stirred for 3.5 hours at 50°C. The resction mixture was allowed to room temperature, and water was added to the system at the same temperature, which was extracted with eithyl acetate. The organic layer was washed with saturated aqueous sodum temperature, which was extracted under a reduced pressure. The residue thus obtained was purified by reverse-phase high performance liquid chromotography (using an acetontritie-water mobile phase containing 0.1% etit/lurocaectic acid), after which triethylamine was added to a mixture of the resulting target product and the mobile phase, thereby rendering the mobile phase basis, and the eluate was concentrated under a reduced pressure. The residue thus obtained was washed with water to obtain the title compound (6.1 mg. 12%).

MS mete 530 344,06/MHP.

⁹ ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.17 (3H, s), 3.86 (2H, s), 3.94 (2H, s), 5.93 (1 H, s), 5.96 (1 H, s), 6.49-6.57 (4H, m), 7.17 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 8.1 Hz), 7.75 (1 H, d, J = 7.1 Hz), 8.38 (1 H, s).

[Example 179] 5-(3-(6-Benzyloxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

25 [1431]

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38 [1432] To a tatrahyrdnuran (7.00 mL) solution of (2-benryloxy-pyridin-5-yh)-acethyydroximoy/chloride (191 mg, 0.890 mm)) discribed in Manufacturing Example 12-15 and 5-ethyyh-pyridin-2-yenine (4.00 mg, 0.399 mmo)) discribed in Manufacturing Example 28-1-3 was added triethylamine (142 µL, 1.02 mmol) under nitrogen atmosphere at room temperature, without was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and died over anythydrous magnetism sullaties, and the solvent was exponented under a reduced pressure. The residue was purified by VH sidica gel column chromatography (ethyl acetate: heptane = 1:1 - 2:1) to tottain the title compound (15.7 mg.).

1H-NMR Spectrum (DMSO-d_b) δ (ppm): 3.94 (2H, s), 5.33 (2H, s), 6.50 (1H, dd, J = 0.8, 8.8 Hz), 6.53 (2H, brs), 6.61 (H, s), 6.85 (HH, d, J = 8.4 Hz), 7.37 (3H, m), 7.427-45 (2H, m), 7.65 (1 H, dd, J = 2.4, 8.4 Hz), 7.75 (1 H, dd, J = 2.4, 8.4 Hz), 2.31 (1 H, d) = 2.4 Hz), 8.42 (Hz), 8.42 (Hz), 9.20 (Hz), 8.42 (Hz), 9.42 (Hz), 8.43 (Hz), 9.43 (Hz), 9.44 (Hz), 9.45 (Hz

[Example 180] 5-(3-(4-(Pyridin-4-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1433]

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[1434] To a letrahydrofuran (3 mL) and accitone (8 mL), solution of 4-(6-(6-aminopydidin-3-yl)-isoxazol-3-yimethyl)-phen (1/55 mg, 0.65 immol) described in Manufacturing Exemple 177-1 was added a 5. No odium hydroded equeous solution (112 µL, 0.661 mmol) at room temperature, which was dissolved by imidating ultrasonic wave for 1 minutes solution (112 µL, 0.661 mmol) at room temperature, which was dissolved by imidating ultrasonic wave for 1 minutes received to the control of the solution of 4-chioromethylpyridine hydrochloride (17 mg, 0.10 mmol) in a solution of 4-chioromethylpyridine hydrochloride (17 mg, 0.10 mmol) in seriahydrofuran (1 mi.) and saturated aqueous solution of 4-chioromethylpyridine hydrochloride (17 mg, 0.10 mmol) in terrahydrofuran (1 mi.) and saturated aqueous solution individe (1 mL), solution of the solution and the partitioning the tetrahydrofuran (1 mi.) added to a dimethyl sulfoxide (1 mL) solution of the solution solution and the partitioning the tetrahydrofuran layer was added to a dimethyl sulfoxide (1 mL) solution of the solution solution of 50°C. Water was added to the readon instruct at room temperature, which was extracted with eithyl acetate. The organic layer was separated, weshed with water and surtured aqueous sodium chiolofic died over anhydrow mangaesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate) to obtain the title compound (2 mg, 23%). H-MNR Spectrum (10 COL) § (5 pm), 38 (2 H, 4), 4 E, (8 H, 5), 58 (2 H, 4), 5, 6 (8 H, 4), 5, 6 (8 H, 4), 5, 6 (8 H, 4), 5, 6 (1 H, 4), 5,

[Example 181] 5-(3-(6-Phenoxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1435]

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2 [1438] To a tetrahydrofuran (2 mL) solution of 5-ethynyl-pyrdin-2-ylamine (30 mg, 0.25 mnol) described in Manufacturing Example 28-1-3 were added (2-phenoxypyrdin-5-yr)-acetohydroximoyl ohloride (100 mg, 0.381 mmol) described in Manufacturing Example 40-1-4 and friethylamine (70.8 µL, 0.506 mmol), which was stirred for 8 hours at 50°C. Water was added to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous amgnesium suifacts, and filtered. The 5 filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate) to obtain the title compound (26 m, 30%).

¹H-NMR Spectrum (DMSO-d_g) δ (ppm):3.97 (2H, s), 6.48 (1H, dd, J = 0.73, 8.6 Hz), 6.52 (2H, s), 6.61 (1 H, s), 6.97 (1 H, d, J = 8.4 Hz), 7.08-7.10 (2H, m), 7.16-7.20 (1 H, m), 7.37-7.41 (2H, m), 7.72-7.77 (2H, m), 8.11 (1 H, d, J = 2.2 Hz), 8.37 (1 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz), 6.73 (2 H, dd, J = 0.73, 2.4 Hz)

[Example 182] 5-(3-(4-(5-Chloro-furan-2-ylmethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1437]

[1438] To a mixture of (4-(5-chloro-turan-2-ylmethyl)-plenyl)-acetohydroximoyl chloride (25 mg, 0.088 mmol) described in Manufacturing Example (62-16 and tetrahydrofuran (1 ml.) were added 5-ethynyl-pydrifo-2-yalmine (8.0 mg, 0.068 mmol) described in Manufacturing Example (28-1-3 and triesthylamine (19 µL, 0.14 mmol), which was stirred for 1 hour at 50°C. The reaction mixture was allowed to room temperature, and water was added to the sextern at the same temperature, which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue thus obtained was purified by reverse-phase high performance liquid chromatography (using an acetonitrile water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound 1.6 ma. 4.9% as a trifluoroacetic acid salt.

MS m/e(ESI) 366.09(MH+)

¹H-NMR Spectrum (DMSO-d_g) δ (ppm): 3.93 (2H, s), 3.96 (2H, s), 6.24-6.25 (1H, m), 6.34-6.35 (1 H, m), 6.71 (1 H, s), 6.76 (1 H, d, J = 8.6 Hz), 7.20 (2H, d, J = 7.9 Hz), 7.25 (2H, d, J = 7.9 Hz), 8.00 (1 H, d, J = 8.6 Hz), 8.42 (1 H, d, J = 2.4 Hz).

[Example 183] 5-(3-(4-(4-Chloro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1439]

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[1440] To 4-(5-(6-amino-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol (20.0 mg, 0.07 mmol) described in Manufaculring texmple 177-11 were added tetrahydrotrura (3 mL) and a 5 N sodium hydroxide aqueous solution (14.9 µL, 0.07 mmol), which was dissolved by irradiating ultrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white solid. To a mixture of the solid obtained above and NN,4-direthylformamide (1 mL) vas added above and NN,4-direthylformamide (1 mL) and classified in N4-mixture place in N4-mixture was colored to come temperature and then partitioned into water and ethyl acetate. The organic layer was separated, washed with water and esturated aqueous sodium chloride, dried over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane : ethyl acetate = 1; 1) to obtain the titls compound (72 mg, 25%).

1H - NMR Spectrum (DMSO-d₀) \(\delta\) (pm): 3.89 (2H, s), 5.15 (2H, s), 6.47 (1 H, d, J = 8.8 Hz), 6.50 (2H, brs), 6.53 (1 H, s), 6.85 (1 H, s), 8.98 (2H, d, J = 8.4 Hz), 7.21 (2H, d, J = 8.4 Hz), 7.48 (1 H, dd, J = 2.4, 5.2 Hz), 7.72 (1 H, dd, J = 2.4, 8.2 Hz), 7.72 (1 H, dd, J = 2.4)

Example 184] 5-(3-(4-(5-Fluoro-pyridin-2-ylmethoxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1441]

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[1442] To 4-(5-(6-amino-pyridin-3-yf)-iscoazol-3-yfmethyl)-phenol (20.0 mg, 0.07 mmol) described in Manufacturing Example 177-11 were added tetrahydrofuran (3 ml.) and a 5 N sodium hydroxide aqueous solution (14.9 µL, 0.07 mmol), which was dissolved by reindating ultrasonic wave for 1 minute. The reaction solution was concentrated under a reduced pressure, which gave a white solid. To a mixture of the solid obtained above and NN-dimethyformamide (1 ml.) was added an NN-dimethyformamide (1 ml.) was added an NN-dimethyformamide (1 ml.) solution of the 2-chloromethyf-5-fluore pyridine (12.0 mg, 0.08 mmol) described in Manufacturing Example 41-12, which was stirred for 1 hour at 60°C. The reaction mixture was cooled to room temperature and then partitioned into water and detylin actetat. The organic layer was sparared, washed with water and startered aqueous sodium chloride, dried over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (heptane: ettly acetate = 1; 1) to obtain the title compound (3.0 mg, 11 %).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.96 (2H, s), 4.73 (2H, brs), 5.16 (2H, s), 6.12 (1H, s), 6.52 (1 H, d, J = 8.8 Hz),

6.93 (2H, d, J = 8.8 Hz), 7.20 (2H, d, J = 8.8 Hz), 7.42 (1H, dt, J = 2.8, 8.4 Hz), 7.49-7.55 (1 H, m), 7.75 (1 H, m), 8.42-8.44 (2H, m).

[Example 185] 5-(3-(6-(2-Fluoro-phenoxy)-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1443]

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HNNN

[1444] To a mixture of (6-(2-fluoro-phenoxy)-pyridin-3-yil)-acetohydroximoyl chloride (28 mg) described in Manufacturing Exemple 74-14 and tealrshydrotimer (1 mt), were added 5-ethrynl-pyridin-2-ylamine (30 mg, 0.076 mm) described in Manufacturing Exemple 28-1-3 and trieftylamine (2 µ Lu, 0.15 mmo), which was estirred for 5 hours at 50°C. 27 The reaction mixture was allowed to room temperature, water was added at the same temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueues sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate) to obtain the title compound (4.6 mg, 17%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 3.98 (2H, s), 4.73 (2H, br s), 6.14 (1 H, s), 6.54 (1 H, dd, J = 0.7, 8.6 Hz), 6.96 (1 H, dJ, J = 8.4 Hz), 7.147.26 (4H, m), 7.63 (1 H, dd, J = 2.6, 8.4 Hz), 7.76 (1 H, dd, J = 2.4, 8.6 Hz), 8.08 (1 H, dd, J = 0.6.2.5 Hz), 8.85 (H J, d.) = 2.4 Hz).

[Example 186] 5-(3-(6-(4-Fluoro-phenoxy)-pyridin-3-vlmethyl)-isoxazol-5-vl)-pyridin-2-vlamine

[1445]

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HN N O O

[1448] To a mixture of (6-(4-fluoro-phenoxyl-prixfiin-34yl-acetohydroximoyl chloride (28 mg) described in Manufacturing Example 75-1-4 and tetrahydroxima (11 mL) were added 5-dethynyl-prixfiin-2-ylamine (6.0 mg, 0.051 mmo) described in Manufacturing Example 28-1-3 and triestlystamine (14 µL, 0.10 mmo), which was stirred for 5 hours at 50°C. The reaction mixture was allowed to room temperature, and the same temperature, and the mixture was extracted with eithyl acetes. The organic layer was washed with seturated equeues sodium chloride, and was conservated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate) to obtain the title compound (3.5 mg, 19%).

1H-NMR Spectrum (CDCl₃) δ (ppm): 3.98 (2H, s), 4.72 (2H, br s), 6.15 (1H, s), 6.54 (1 H, dd, J = 0.7, 8.6 Hz), 6.88 (1 H, d, J = 8.6 Hz), 7.65-7.12 (4H, m), 7.62 (1 H, dd, J = 2.6, 8.4 Hz), 7.77 (1 H, dd, J = 2.2, 8.6 Hz), 8.12 (1 H, d, J = 2.6 Hz), 8.45 (1 H, d, J = 2.4 Hz).

[Example 187] 6-Methyl-5-(3-(4-(pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1447]

[1448] To a mixture of (4-(pyridin-2-yloxymethyl)-phenyl)-acetohydroximoyl chloride (55 mg, 0.20 mmol) described in Manufacturing Example 2-1-5 and tetrahydrofuran (1 mL) were added 5-ethynyl-6-methyl-pyridin-2-ylemine (20 mg, 0.15 mmol) escribed in Manufacturing Example 187-1-2 and tribrylamine (43 al., 0.31 mmol), which was street of 25 hours at 50°C. The reaction mixture was allowed to room temperature, and water was added thereto at the same temperature, which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium biolifice, and was concentrated under a reduced pressure. The residue thus obtlanded was purified by NH sillicag ethyl statement of the st

column chromatography (hoptane: ethyl accetate = 1: 2) to obtain the title compound (35 mg, 61 °k).

H-MMR Spectrum (CDCl) § (ppm): 222 (8H, s), 406 (2H, s), 4.86 (2H, br s), 5.36 (2H, s), 6.05 (1H, s), 8.04 (1H, d, J = 8.4 Hz), 67.96-8.81 (1H, m), 687-6.80 (1H, m), 7.31 (2H, d, J = 8.1 Hz), 7.43 (2H, d, J = 7.9 Hz), 7.56-7.60 (1H, m), 7.41 (1H, J, J = 8.4 Hz), 8.15-8.18 (1H, m)

[1449] The starting material, 5-ethynyl-6-methyl-pyridin-2-ylamine, was synthesized as follows.

[Manufacturing Example 187-1-1] 6-Methyl-5-trimethylsilanylethynyl-pyridin-2-ylamine

[1450]

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H,N N

[1451] To a mixture of 6-amino-3-brono-2-methylpyridine (200 mg, 1.0 mmol), trimethylsilylacetylene (0.22 mL, 1.8 mmol), copper (f) loddie (8.9 mg, 0.62 mmol), and 1.4-dioxane (1.5 mL) was added bistriphenylphosphine/plealladium (f) chioride (7.8 mg, 0.10 mmol), wish was stirred under nitrogen entresphere for 3 hours and 30 minutes at 100°C. The reaction mixture was allowed to room temperature, water was added to the reaction mixture at the same temperature, water was added to the reaction mixture at the same temperature chyl acetate was added, and the mixture was filtered through a Cellite pad. The organic layer of the filtrate was separated and washed with seturated aqueous sodium chloride, and was concentrated under a reduced pressure, and the residue thus obtained was purified by silica gal column chromatography (heptane: ethyl acetate = 2: 1) to obtain the title compound (14.0 mg, 27%, purity, 68%).

¹⁶ 1H-NMR Spectrum (CDCl₂) δ(ppm): 0.24 (9H, s), 2.50 (3H, s), 4.59 (2H, brs), 6.26(1H,d, J=8.2 Hz), 7.44(1H,d,J=8.4 Hz).

[Manufacturing Example 187-1-2] 5-Ethynyl-6-methyl-pyridin-2-ylamine

[1452]

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[1453] To a mixture of 6-methyl-5-trimethylsilanylethymyl-pyridin-2-ylamine (450 mg, 1.9 mmol) described in Manufacturing Example 187-1-1 and methanol (6 ml.) was added potassium carbonate (390 mg, 2.8 mmol), which was stirred for 30 minutes at the same temperature. Water was added to the reaction mixture, which was extracted with rely acetate. The organic layer was washed with saturated equeous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl acetate = 1:1) to obtain the title compound (290 mc 88%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.52 (3H, s), 3.24 (1 H, s), 4.58 (2H, br s), 6.29 (1 H, d, J = 8.4 Hz), 7.47 (1 H, d, J = 8.4 Hz).

© [Example 188] 5-(3-(4-Benzyloxy-benzyl)-isoxazol-5-yl)-6-methyl-pyridin-2-ylamine

[1454]

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[1455] To a mixture of 4-benzyloxy-phenyl-seatohydroximoyl chloride (69 mg. 0.21 mmol) described in Manufacturing Example 1-13 and tetrahydrotime (1 mL) were adodd 5-tdhynyl-6-morthy-pyridin-2-lyamine (22 mg. 0.15 mmol) described in Manufacturing Example 187-1-2 and triethylamine (46 µL, 0.33 mmol), which was stirred for 2 hours at 50°C. The reaction mixture was allowed to room temperature, water was added at the same temperature, and the mixture was extracted with early acetate. The organic layer was weshed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue thus obtained was purified by NH silica gel column chromatography (heptane : ethyl scattae 1 : 12 to obtain the title compound (35 mg. 57%).

H-NMR Spectrum (CDCl₂) δ (ppm): 2.52 (3H, s), 3.99 (2H, s), 4.80 (2H, br s), 5.05 (2H, s), 6.04 (1 H, s), 6.39-6.41 (1 H, m), 6.92-6.96 (2H, m), 7.19-7.23 (2H, m), 7.30-7.44 (5H, m), 7.75 (1 H, d, J = 8.4 Hz).

[Example 189] 3-(5-(4-(Pyridin-2-ylmethoxy)-benzyl)-isoxazol-3-yl)-pyridin-2-ylamine

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[1457] To a N-methypymrollionne (4 mL), solution of 5-chloro-3-(5-(4-(pyridin-2-ylmathoxy)-boxx2)/-8-(oxzo/3-yl-)-yl-oxzo/3-yl-)-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo/3-yl-oxzo-yl-oxzo/3-yl-oxzo-yl-oxzo/3-yl-oxzo-yl-oxzo/3-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo-yl-oxzo

1H-NMR Spectrum (CDCl₂) & (ppm):4.07 (2H, s), 5.21 (2H, s), 6.24 (1 H, s), 6.25 (2H, s), 6.66 (1 H, dd, J = 4.9, 7.7 Hz), 6.96-7.00 (2H, m), 7.20-7.25 (3H, m), 7.25 (1 H, d, J = 7.9 Hz), 7.64 (1 H, dd, J = 1.7, 7.5 Hz), 7.72 (1 H, dt, J = 1.8, 7.7 Hz), 8.11 (1 H, dJ, J = 1.7, 4.8 Hz), 8.59-8.61 (1 H, m).

[1458] The starting material, 5-chloro-3-(5-(4-(pyridin-2-ylmethoxy)-benzyl)-isoxazol-3-yl)-pyridin-2-ylamine, was synthesized as follows.

[Manufacturing Example 189-1-1] 4-(3-(2-Amino-5-chloro-pyridin-3-vl)-isoxazol-5-vlmethyl)-phenol

[1459]

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[1460] To a trifluoroaceito acid (6 mL) solution of 3-(6-(4-benzyloxy-benzyl)-soxazol-3-yl)-5-chioro-pyridin-2-ylamine (304 mg. 0.776 mmol) escribed in Mauntacturing Example 20-2-3 was acided thiosanised (684 mL, 3.10 mmol) at 0°C, which was stirred for 3 hours at room temperature. To this reaction mixture were added sodium hydrogencarbonate and water at 0°C, which was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated acqueous sodium-chioride, died over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was unprified by NH silica gel column chromatography (ethyl acetate: methanol = 20: 11) to obtain the title compound (146 mg. 62%).

⁵ ¹H-NMR Spectrum (DMSO-d₆) & (ppm):4.07 (2H, s), 6.74 (2H, d, J = 8.4 Hz), 6.98 (1 H, s), 7.07 (2H, s), 7.12 (2H, d, J = 8.4 Hz), 8.09 (1H, d, J = 2.6 Hz), 8.13 (1H, d, J = 2.6 Hz), 9.36 (1 H, s).

[Manufacturing Example 189-1-2] 5-Chloro-3-(5-(4-(pyridin-2-ylmethoxy)-benzyl)-isoxazol-3-yl)-pyridin-2-ylamine

0 [1461]

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[1462] To a tetrahydrotran (a mL) solution of 4-(3-(2-amino-5-chloro-pyridin-3-yl)-isoxazol-5-ymeatyl)-phenol (146 mg, 0.484 mmol) described in Manufacturing Example 189-1-1 was added a 5 N sodium hydroxide aqueous solution (98.8 μL, 0.484 mmol) at commune there are under the was dissolved by irradiating ultrasonic wave for 1 minute. The reaction mixture was concentrated under a reduced pressure to obtain a sodium sait. A tetrahydrotran solution of 2-picolyticoride hydrochloride (198 mg, 1.21 μmol) in tetrahydrotran (2 mL) water (2 mL), stirring for 1 minute, and then separating the tetrahydrotran eye was added at room temperature on an NA-dimethydromamide (6 mL) solution of the sodium sait obtained above, which was stirred for 2 hours at 60°C. Water was added to the reaction mixture at room temperature, which was stracted with ethyl scatals. The organic layer was separated, washed with water and saturated aqueous sodium chridred, eried over anhydrous magnesium suifleta, and filtered. The filteriate was concentrated under a reduced pressure, and the residue was nurfied by NH silica gel column chromatography (heptane : ethyl acetate = 1: 1) to obtain the stile compound (141 mg, 74%).

¹H-NMR Spectrum (CDCL), 8 (ppm):4.08 (2H, s), 5.22 (2H, s), 6.22 (1H, s), 6.25 (2H, s), 6.99 (2H, d, J = 8.6 Hz), 7.22 (2H, d, J = 8.1 Hz), 7.28-7.31 (1 H, m), 7.54 (1 H, d, J = 6.4 Hz), 7.80 (1 H, d, J = 2.4 Hz), 7.73 (1 H, dt, J = 1.8,7.9 Hz), 8.77 (1 H, dt, J = 2.4 Hz), 6.87 (1 H, d, J = 4.4 Hz), 8.87 (1 Hz), 8.87 (

[Example 190] 2-Methyl-5-(3-(4-(pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridine

[1463]

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1464] To a tetrahydrofuran (2mL) solution of 5-ethymi-2-mathyl-pyridine (10 mg, 85 µmol) deacr fibed in Marufacturing Example 190-11- were added-4 (gyridin-2-yloxymethyl)-phenyl-acetohydroxiny-chloride (31 mg, 0.11 mmol) deacr fibed in Manufacturing Example 2-1-3 and triethylarinine (18 µL, 0.13 mmol), which was sitrared for 2 hours and 30 minutes at 50°C. Water was added to the reaction mixture at from temperature, which was extracted with ethyl acetrac. The organic layer was weaked with saturated a quoesus sodium choinde, died do ver enhydrous magnesium sulfate, and filtered. The filtrared was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl scattae 1 : 1) to botain the title compound (14 mg, 46%).

1H-MMR Spectrum (DMSO-4₃) 6 (ppm):2.52 (3H, s), 4.05 (2H, s), 5.32 (2H, s), 6.85 (1 H, d, J = 8.2 Hz), 6.96 (1 H, s), 6.96 (1 H, s), 6.96 (1 H, dd, J = 5.1, 6.6 Hz), 7.33 (2H, d, J = 8.1 Hz), 8.739-7.43 (3H, m), 7.69-7.74 (1 H, m), 8.10 (1 H, dd, J = 2.2, 8.1 Hz), 8.17 (1 H, dd, J = 2.0, 5.1 Hz), 8.91 (1 H, d, J = 2.2 Hz).

[1465] The starting material, 5-ethynyl-2-methyl-pyridine, was synthesized as follows.

[Manufacturing Example 190-1-1] 5-Ethynyl-2-methyl-pyridine

[1466]

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[1467] To a N-methylpyrrolidinone (20 mL) solution of 5-bromo-2-methyl-pyridine (1.00 g, 5.81 mmol) were added trimethylalylacetylene (1.23 mL, 8.72 mmol), stenkie (triphenylphosphine)palladium (0) (134 mg, 0.116 mmol), copper (1) (oldide (44.3 mg, 0.232 mmol), and N.N. discoprophylenylamic) (20 mL, 1.15 mmol), which was streduced and N.N. discoprophylenylamic) (20 mL, 1.15 mmol), which was streduced real national managements of the second stream of the second stream

¹H-NMR Spectrum (CDCl₃) δ (ppm):2.57 (3H, s), 3.17 (1 H, s), 7.12 (1 H, d, J = 8.1 Hz), 7.66 (1 H, dd, J = 2.0, 8.1 Hz), 8.61 (1 H, d, J = 1.8 Hz).

[Example 191] 3-(1-(6-Benzyloxy-pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-pyridin-2-ylamine

[1468]

[1469] To an N,4 dimethylformanide (5.00 mL) solution of 3-(1H-pyrazol-4-yl)-pyridin-2-ylamine (2.0.0 mg. 0.126 mmol) described in Manufacturing Example 32-1-4 was added sodium hydride (5.50 g. 0.138 mmol, 60% in oil) on an ice bath (0°C) under nitrogen atmosphere, which was stirred for 30 minutes at room temperature. Thereafter, 2-benzyloxy-5-chloromethyl-pyridine (49.7 mg. 0.213 mmol) described in Manufacturing Example 191-12 was added to this mixture, which was stirred for 30 minutes at room temperature. The institute was partitioned into they decette and water at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over anhydrous magnesium suitriae, and the solvent was everporated under a reduced pressure. The restate was purified by NH silica gel column chromatography (ethyl sociate: heptane = 2:1 → ethyl sociate) to obtain the title compound (31.3 mg, 70.1 %). "H-HMR Spectrum (DMSO-d₃) 8 (ppm): 5.30 (2H, s), 5.37 (2H, s), 5.87 (1H, d, s), 4.8.7, 7.27 (1H, dd, J = 2.0, 4.8 Hz), 8.71 (1H, d, J = 0.8 Hz), 8.87 (1H, dd, J = 2.0, 4.8 Hz), 8.18 (1H, d, J = 0.8 Hz), 8.87 (1H, dd, J = 2.0, 4.8 Hz), 8.18 (1H, d, J = 0.8 Hz), 8.20 (1H, d, J = 2.8 Hz).

[Manufacturing Example 191-1-1] (6-Benzyloxy-pyridin-3-yl)-methanol

[1471]

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[1472] To a methanol (20.0 mL) solution of 6-benzyloxy-pyridine-8-carbatiehyda (2.00 g, 9.38 mmol) described in 6 Manufacturing Example 12-1-2 was added sodium borehydride (428 mg, 11.3 mmol) on an ice bath (0°C) under nitrogen atmosphere, which was stirred for 10 minutes at room temperature. Water was added to the reaction mixture at room temperature, which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium critical and rided over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure to obtain the title compound (1.84 g, 91.1%).

¹H- NMR Spectrum (CDCl₃) δ (ppm): 4.55 (2H, s), 5.39 (2H, s), 6.82 (1 H, d, J = 8.4 Hz), 7.30-7.45 (5H, m), 7.63-7.66 (1 H, m), 8.16 (1 H, d, J = 2.4 Hz).

[Manufacturing Example 191-1-2] 2-Benzyloxy-5-chloromethyl-pyridine

5 [1473]

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[1474] To a dichloromethane (4.00 mL) solution of (6-benzy/oxp-pyridin-3 yt)-methanol (1.80 g, 8.36 mmol) described in Manufacturing Example 191-11 was added drow/wes thirdyny/chioride (723 Lu, 1.00 mmol) on an ice bath (0°C) under nlorgen atmosphere, which was strined for 5 minutes at room temperature. Aqueous sodium bicarbonate was added to the reaction solution, which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous southoring the control of the control of

 1 H-NMR Spectrum (CDCl₃) 3 (ppm) : 4.60 (2H, s), 5.37 (2H, s), 6.80 (1H, d, J = 8.4 Hz), 7.31-7.46 (5H, m), 7.61-7.63 (1 H, m), 8.11 (1H, d, J = 2.4 Hz).

[Example 192] 3-(1-(4-(Pyridin-2-vlmethoxy)-benzyl)-1 H-pyrazol-4-vl)-pyridin-2-vlamine

[1475]

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NNN NH,

[1476] 2-(4-chloromethyl-phenoxymethyl)-pyridine was obtained according to the methods similar to those of Manufacturing Example 199-1-1 and Manufacturing 199-1-2 using 4-(pyridine 2-ylmethoxy)-benzaidehyde described in Manufacturing Example 203-1-1.

[1477] To an N.N-dimethyformamide (5.00 mL) solution of 3-(1 H-pyrazol-4-yl)-pyridin-2-ylamine (20.0 mg. 0.126 mm) described in Manufacturing Example 32-14 was added sodium hydride (5.50 mg. 0.138 mm.e, 06% in oil) on an loe bath (PC) under nitrogen atmosphere, which was stirred for 30 minutes at room temperature. Thereafter, 2-d-toromathyl-benzyloxyl-pyridine (48.7 mg, 0.213 mm.oi) described in Manufacturing Example 30-1-1 was added to the above mixture, which was stirred for 30 minutes at room temperature. This mixture was partitioned into eithyl acetate and water at room temperature. The organic layer was washed with water and saturated aqueous sodium chieride and dired over anilydrous megnesium suitte, and the solvent was exported under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 2:1 → ethyl acetate) to obtain the title compound (2.19 mg. 49.0%). 2-t-chromethyl-phenoxymethyl-pyride.

1H-NMR Spectrum (CDCl₃) δ (ppm) : 4.56 (2H, s), 5.21 (2H, s), 6.95-6.99 (2H, m), 7.21-7.23 (1 H, m), 7.29-7.32 (2H, m), 7.49-7.51 (1 H, m), 7.69-7.73 (1 H, m), 8.59-8.61 (1H, m).

the title compound

1-H-NMR Spectrum (DMSO-d₆) 8 (ppm): 5.16 (2H, s), 5.26 (2H, s), 5.59 (2H, brs), 8.61 (1 H, dd, J=5.2, 7.2 Hz), 6.99-7.02 (2H, m), 7.26-7.29 (2H, m), 7.32-7.35 (1 H, m), 7.46-7.50 (2H, m), 7.74-1 (1 H, s), 7.80-7.84 (1 H, m), 7.84-7.87 (1 H, m), 8.13 (1 H, d, J=1.2 Hz), 8.56-5.86 (1 H, m).

[Example 193] 3-(1-(6-Phenoxy-pyridin-3-vlmethyl)-1H-pyrazol-4-vl)-pyridin-2-vlamine

[1478]

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[1479] To an N-N-dimethylformamide (5.00 mL) solution of 3-(1/E-pyrazot-4-y)-pyridin-2-ylamine (20.0 mg. o.128 mmol) described in Manufacturing Example 32-1-4 was added sodium hydride (5.50 mg. o.138 mmol, 60% in oil) on an ice ball (0°C) under nitrogen atmosphere, which was stirred for 10 minutes at room temperature. Thereafter, 5-chloromethyl-2-phenoxy-pyridine (49.7 mg. o.228 mmol) described in Manufacturing Example 193-1-2 was added to the above mixture, which was stirred for 30 minutes at morn temperature. The reaction mixture was partitioned into ethyl acetate and water at room temperature. The organic layer was washed with water and saturated a queous sodium chloride and dried over anthydrous magnesium sulfate, and the solvent was exponented under a roduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 2 : 1-> ethyl acetate) to obtain the title compound (25.0 mg. 58.2%).

¹H-NMR Spectrum (DMSO-d_s) δ (ppm): 5.34 (2H, s), 5.62 (2H, brs), 6.61 (1 H, dd, J = 4.8, 7.6 Hz), 7.01 (1 H, d, J = 8.4 Hz), 7.10-7.12 (2H, m), 7.19-7.23 (1 H, m), 7.39-7.43 (2H, m), 7.48 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.67 (1H, s), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2.0, 7.2 Hz), 7.83 (1 H, dd, J = 2

H, dd, J = 2.4, 8.4 Hz), 7.87 (1 H, dd, J = 2.0, 5.2 Hz), 8.16 (1 H, d, J = 2.8 Hz), 8.19 (1 H, s). [1480] The starting material, 5-chloromethyl-2-phenoxy-pyridine, was synthesized as follows.

[Manufacturing Example 193-1-1] (6-Phenoxy-pyridin-3-yl)-methanol

[1481]

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[1482] To a diethyl ether (20.0 m.l.) solution of 5-bromo-2-phenoxy-pyridine (1.02 g. 4.08 mmnl) described in Manufacturing Example 40-1-1 was added dropwise n-butyl filthium (2.55 M n-bexane solution, 1.92 ml., 4.90 mmol) on a dry ice ethanol bath (78°C) under nitrogen amosphere, which was stirred for 30 minutes at 78°C. Thereafter, N.N-dimethylformamide (378 µ.L., 4.90 mmol) was added dropwise, which was stirred for 10 minutes at 78°C. Then, sodium borohydride (3.09 mg., 8.16 mmol) and methanol (15.0 ml.) were added, which was stirred for 50 minutes at rom temperature. Water was added to the reaction mixture, which was extracted with ethyl scetate. The organic layer was washed with saturated aqueous sod mirchiodle, and the solvent was exported under a reduced pressure. The residue was purified by slicia gel column chromatography (ethyl scetate: heptane = 1: 1) to obtain the tittle compound (2.93 g. 66.5%). 11-NMR Spectrum (CDCl₂) 6 (ppm.): 4.62 (2H₁ g.), 6.88 (1 H., d., J. = 8.4 Hz), 7.10-7.13 (2H, m), 7.18-7.22 (1 H, m), 7.37-7.41 (2H, m), 7.70-7.73 (1 H, m.), 8.12-8.13 (1 H, m.).

[Manufacturing Example 193-1-2] 5-Chloromethyl-2-phenoxy-pyridine

[1483]

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[1484] To a dichloromethane (5.00 mL) solution of (6-phenoxy-pyridin-3-yl)-methanol (488 mg, 2.28 mmol) described in Manufacturing Example 193-1-1 was added dropwise thionyl-chloride (333 µL, 4.56 mmol) on an ice bath (0°C) under nitrogen atmosphere, which was stirred for 5 minutes at room temperature. Aqueous sodium bicarbonate was added to the reaction solution at room temperature, which was extracted with ethyl acetata. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure to obtain the title compound (450 mg, 89.8%).

¹H-NMRSpectrum (CDCl₃) δ (ppm): 4.55 (2H, s), 6.91 (1H, d, J = 8.8 Hz), 7.12-7.15 (2H, m), 7.20-7.24 (1 H, m), 7.38-7.43 (2H, m), 7.72-7.75 (1 H, m), 8.17 (1 H, d, 2.4 Hz).

[Example 194] 3-(1-(4-Prop-2-ynyloxymethyl-benzyl)-1 H-pyrazol-4-yl)-pyridin-2-ylamine

[1485]

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[1486] To a mixture of 3-(114-pyrazol-4-yl)-pyridine2-ylamine (30 mg, 0.19 mmo) described in Manufracturing Example 32-1-4 and tetrahydrofuran (1 mL) was added sodium hydride (12 mg, 0.24 mmol, 50% in oil) at 0°C, and then N,N-dimethylformamide (1 mL) was added. The reaction mixture was stirred for 10 minutes at room temperature, after which 1-chloromethyl-4-prop 2-pyriloxymethylberozene (47 mg, 0.24 mmol) described in Manufracturing Example 194-12 was added to this mixture at 0°C, which was stirred for 5 moust at room temperature. Water was added to the reaction mixture,

which was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 4: 1) to obtain the title commound (37 mp. 62%).

1H-NMR Spectrum (CDCl₃) 5 (ppm): 2.47 (1H, t, J = 2.4 Hz), 4.18 (2H, d, J = 2.4 Hz), 4.56 (2H, br s), 4.61 (2H, s), 5.35 (2H, s), 6.70 (1 H, dd, J = 5.0, 7.4 Hz), 7.28 (2H, d, J = 8.2 Hz), 7.36-7.40 (8H, m), 7.58 (1 H, d, J = 0.7 Hz), 7.74 (1 H, d, J = 0.9 Hz), 2.18 (1 H, d, J = 1.8, 4.9 Hz).

[1487] The starting material, 1-chloromethyl-4-prop-2-ynyloxymethyl-benzene, was synthesized as follows.

[Manufacturing Example 194-1-1] (4-Prop-2-ynyloxymethyl-phenyl)-methanol

[1488]

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[1489] To a mixture of sodium hydride (a00 mg, 8.4 mmn), 50% in oil) and tetrahydroturan (30 mL) was added 1.4 benzenedimehanol (2.3 g, 17 mmo)) at 0°C, and then N,N-dimethylformamide (30 mL) was added. The reaction mixture was stirred at room temperature for 10 minutes, after which propargyl bromide (1.0 g, 8.4 mmol) was added droowise to the reaction mixture at 0°C. The reaction mixture was stirred at room temperature for 1 hour, after which water was added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was washed and saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The resibute thus obtained was purified by NH silics gel column chromatography (heptane: ethyl acetate = 3: 2) to obtain the title compound (860 mg, 58%).

H-HMRS Sockrum (COCA) & formation; 1.64 (H, H, 1. e) = 0, Hz) 2.47 (H, H, L, e) = 2.4 Hz), 4.82 (H, J, e) = 2.4 Hz), 4.82

[Manufacturing Example 194-1-2] 1-Chloromethyl-4-prop-2-ynyloxymethyl-benzene

(2H, s), 4.70 (2H, d, J = 5.9 Hz), 7.37 (4H, s),

30 [1490]

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[1491] A mixture of (4-prop-2-ynyloxymethyl-phenyly-methanol (190 mg, 1.1 mmol) described in Marufacturing Example 194-1-1, triphenylphosphine (340 mg, 1.3 mmol), and carbon tetrachloride (3 mL) was stirred for 6 hours under reflux. The reaction mixture was cooled to room temperature, after which the reaction mixture was concentrated under a reduced pressure. The residue was purified by neutral silica gel column chromatography (ethyl acetate: heptane = 1: 10) to obtain the title compound (180 mg, 84%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.47 (1 H, t, J = 2.4 Hz), 4.18 (2H, d, J = 2.4 Hz), 4.59 (2H, s), 4.62 (2H, s), 7.35-7.40 (4H, m).

45 [Example 195] 3-(1-(4-Cyclopropylmethoxymethyl-benzyl)-1*H*-pyrazol-4-yl)-pyridin-2-ylamine

[1492]

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[1493] To a mixture of 3-(1-(4-bromo-benzy))-1H-pyrazol-4-yl)-pyridin-2-ylamine (24 mg, 0.073 mmol) described in

Manufacturing Example 195-1-1 and 1,4-dioxane (1.5mL) were added water (150 µL), cestium carbonate (95 mg, 0.28 mmol), sedium cyclopropyinherhoymethyl frilluphorborate (19 mg, 0.11 mmol) described in Manufacturing Example 195-2-2, palladium (II) acetate (1.6 mg, 0.0073 mmol), and (±)-2,2-bis(diphenylphosphino)-1,1' binaphthyl (4.5 mg, 0.0073 mmol) at room temperature, which was stirred for 6 hours at 100°C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, after which water and ethyl acetate were added and the mixture was filtered through a Cellite pad. The organic layer of the filtrate was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The readule thus obtained was purified by reverse phase high performance liquid chromatography (using an acetonitrie-water mobile phase containing ol. 1% trifluoroacetic acid), after which tri-terlyramine was added to a mixture of the resulting target product and the mobile phase, thereby rendering the mobile phase basic, and the solvent was evaporated under a reduced pressure. The residue thus obtained was filtered through NH silica que (divin) accetate to botain the title compound (1.6 mg, 6.5%).

MS m/e(ESI) 335.30(MH+) [1494] The starting material, 3-(1-(4-bromo-benzyl)-I H-pyrazol-4-yl)-pyridin-2-ylamine, was synthesized as follows.

5 [Manufacturing Example 195-1-1] 3-(1-(4-Bromo-benzyl)-1H-pyrazol-4-yl)-pyridin-2-ylamine

[1495]

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[1496] To a mixture of 24 (H-pyrazol-4-yl-pyrdin-2-ylamine (150 mg, 0.94 mm.ol) described in Manufacturing Example 32-14 and letrahydrofurar (2 m.) was added soldmin hydride (12 m.) 0.24 mm.ol, 50% in oil) at 0°C, and then N.N-dimethylformamide (2 m.) was added. The reaction mixture was stirred for 10 minutes at room temperature, after which 4-bromohearyl bromide (260 m.), 10 mmol) was added at 0°C to this mixture, which was stirred for 1 brou at room temperature. Water was added to the reaction mixture, which was extracted with eithyl acetate. The organic layer was washed with saturated aquous exodium chloride, and was concentrated under a reduced pressure. The residue was purified by NH allica get column chromatography (ethyl acetate: heptane = 4:1) to obtain the title compound (270 mg, rescu.)

11--MMR Spectrum (CDCl₂) 8 (ppm): 4.55 (2H, brs), 5.30 (2H, s), 6.71 (1 H, ddd, J = 0.7, 4.9, 7.3 Hz), 7.16 (2H, d, J = 8.6 Hz), 7.40 (1 H, d, J = 1.7, 7.3 Hz), 7.50 (2H, d, J = 8.4 Hz), 7.60 (1 H, s), 7.75 (1 H, s), 8.02 (1 H, dd, J = 1.7, 4.9 Hz). [1497] The starting material, sodium cyclopropylmethoxymethyl trifluoroborate, was synthesized as follows.

[Manufacturing Example 195-2-1] 2-(Bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[1498]

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[1489] To a mixture of triiscorpoy/borste (20 g. 110 mmol), dibromomethane (8.6 mL, 120 mmol), and tetrahystrofuran (150 mL) was added dropvise n-bully filthum (2.6 Mn -hexans solution, 38 mL, 100 mmol) over a period of 1.5 hours at 1-78°C, and then the reaction mixture was stirred for 1.5 hours at the same temperature. This mixture was then stirred for 2 hours at room temperature, after which it was cooled to 0°C, methanesulonic acid (6.5 mL, 100 mmol) was added to the reaction mixture, and the reaction mixture was stirred for 1 hour at room temperature. The mixture was cooled to 0°C, pinacol (12 g. 100 mmol) was added to the reaction mixture, and the reaction mixture was then stirred for 1 hour at room temperature. The reaction mixture was cooled are reduced pressure, after which the residue thus obtained was distilled under a reduced pressure (74 - 76°C, 8 mmHg) to obtain the title compound (16 g).

11-NNIR Spectrum (CDCl.) § (0pm. 1: 29 (1214, 8), 250 (214, 8).

[Manufacturing Example 195-2-2] Sodium cyclopropylmethoxymethyl trifluoroborate

[1500]

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[1501] To a mixture of sodium hydride (430 mg, 12 mmol, 86% in oil) and tetrahydroturan (20 mL) was asided cyclo-propylmethanol (1,2 mL, 15 mmol) at 0°C, and the reaction mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added 2-(bromomethyl)-4,4,5-fetramethyl-1,3,2-diousobraice (2.0,9,1 mmol) described in Manufacturing Example 195-2-1 at 0°C, and the reaction mixture was stirred for 1 hour at room temperature, and then for 4 hours at 5°C. The reaction mixture was cooled to 0°C, softim hydrogentiloxide (2.2,9,8 mmol) was added, at 15 the water (15 mL) was added dropwise to the reaction mixture at the same temperature. The reaction mixture was raised to room temperature, after which the solvent was evaporated under a reduced pressure. Acottone (100 mL) and methanol (1 m) were added to the residue thus obtained, which was heated and then gradually cooled to about 40°C, and then filtered. The filtrate was concentrated under a reduced pressure, and the residue was washed with ethyl acetate to obtain the title combound (12.9).

1H-NMR Spectrum (DMSO-d₆) \(\delta\) (ppm): 0.05-0.09 (2H, m), 0.35-0.40 (2H, m), 0.86-0.96 (1 H, m), 2.46 (2H, q, J = 5.6 Hz), 3.00 (2H, d, J = 6.8 Hz).

[Example 196] 3-(1-(4-Ethoxymethyl-benzyl)-1H-pyrazol-4-yl)-pyridin-2-ylamine

25 [1502]

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[1503] To a mixture of 3-(1-(4-bromo-benzy)-11-Frynzao(1-4y)-pyridin-2-ylemine (24 mg, 0.073 mmol) described in Manutacturing Exemple 195-1-1 and 1.4-dioxane (1.5 mL), were added water (150 µL), ossium carbonate (95 mg, 0.23 mmol), the potassium entroxymethyl trifluoroborate (18 mg, 0.11 mmol) described in Manutacturing Exemple 196-1-2, palladium(II) acetate (1.6 mg, 0.0073 mmol), and (±)-2,2-bis (diphenylphosphino)-1,1-binaphthyl (4.5 mg, 0.0073 mmol) are trom temperature, which was stirred under nitrogen atmosphere for 6 hours at 100°C. The reaction mixture was cooled to room temperature, after which water and ethyl acetate were added and the mixture was filtered through a Cellite pad. The organic layer of the filtrate was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue thus obtained was purified by reverse-phase high performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (5.2 mg, 17/3) as a trifluoroacetic acid alst.

MS m/e(ESI) 309.29(MH+)

[1504] The starting material, potassium ethoxymethyl trifluoroborate, was synthesized as follows.

[Manufacturing Example 196-1-1] Tributyl-ethoxymethyl-tin

[1505]

[1506] To a mixture of disopropylamine (2.1 ml., 15 mnol) and tetrahydroturan (30 ml.) was added dropwise n-buty lithium (2.4 M n-hexane solution, 50 ml., 12 mmol) at 78°C, and then the reaction mixture was stirred for 30 minutes. Tributytin hydride (3.3 ml., 12 mmol) was added dropwise to this mixture at 78°C, and then the reaction mixture was stored for 40 minutes at 0°C. The reaction mixture was cooled to 78°C, after which ethoxymethyl chloride (1.1 ml., 12 mmol) was added dropwise to the reaction mixture. The reaction mixture was raised to room temperature, dethyl ether and an ammonium chloride aqueous solution were added to the reaction mixture, and the organic layer was separated. The organic layer was washed with saturated aqueous solution chloride, after which the organic layer was concentrated under a reduced pressure. The residue was purified by returnal silica gel column chromatography (heptane: dethyl ether = 30: 1) to obtain the title compound (2.8, 66%).

H-NMIR Sockerum (CDCL) & formit 0.87°0.92 (15H. m.) 1.16 (3H. t. 1.2 7.0 Hz), 1.26-1.35 (6H. m.) 1.45-1.56 (6H. m.).

3.36 (2H, q, J = 7.0 Hz), 3.74 (2H, t, J = 6.5 Hz).

[Manufacturing Example 196-1-2] Potassium ethoxymethyl trifluoroborate

[1507]

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[1508] To a mixture of tributyl-ethoxymethyl-lin (1.0 g, 2.9 mmol) described in Manufacturing Example 196-1-1 and strahydrofurun (1 om L) was added dropwise n-buyl filbium (1.6 h. n-beans solution, 2 off. 1.3 cm) at 1.7 mixture was stirred for 30 minutes at the same temperature. To a mixture of trilapopropyl borate (0.73 mixture such as stirred for 30 minutes at the same temperature. To a mixture of trilapopropyl borate (0.73 mixture such as stirred for 30 minutes at room temperature. Potassium hydrogenfluoride (1.3 g, 17 mmol) was added at 0°C to the mixture, and then water (10 mL) was added dropwise to the reaction mixture. The reaction mixture was oncentrated under a reduced pressure. The residue thus obtained was washed with diethyl either (50 mL). Acetone (100 mL) was added to this residue, which was filtered. The filtrate was concentrated under are reduced pressure, and the residue was recrystallized from acetonitrie to obtain the title compound (150 mg, 32%).

11-HMMS Descrim (DMSO-04.) 8 (porm): 0.99 (3H t, J = 7.0 Hz). 2.42 (2H, q, J = 5.6 Hz), 3.18 (2H, q, J = 7.0 Hz).

[Example 197] 3-(1-(4-Cyclobutoxymefhyl-benzyi)-1H-pyrazol-4-yl)-pyridin-2-ylamine

[1509]

[1510] To a mixture of 3-(1-(4-bromo-beazy)-11-typyzac/1-4y)-pyrdin-2-ylamine (24 mg, 0,073 mmol) described in Manufacturing Example 195-1-1 and 1,4-dioxane (1.5mL) were added water (150 µL), cessium carbonate (95 mg, 0.23 mmol), potassium oyclobutosymethyl trifluoroborate (21 mg, 0.11 mmol) described in Manufacturing Example 197-1-2, palladium(II) sectate (1.6 mg, 0.0073 mmol), and (±)-2.2-bis(diphenylphosphino)-1,1*-binaphthyl (4.5 mg, 0.0073 mmol) are trom temperature, which was stirred under introduce atmosphere for 6 hours at 100°C. The reaction mixture was

cooled to room temperature, after which water and ethyl acetate were added and the mixture was filtered through a Cellic pad. The organic layer of the filtrate was washed with saturated aqueous sodium chloride, and was concentrated under a reduced pressure. The residue thus obtained was purified by reverse-phase high performance liquid chromatography (using an acedonitrile-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (5.2 m. 18%) as influoroacetic acid saft.

MS m/e(ESI) 335.19(MH+)

[1511] The starting material, potassium cyclobutoxymethyl trifluoroborate, was synthesized as follows.

[Manufacturing Example 197-1-1] Tributyl-cyclobutoxymethyl-tin

[1512]

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[1613] To a mixture of sodium hydride (250 mg, 7.0 mmol, 66% in oil) and tetrahydroturan (20 mL) were added cylobutanol (0.55 mL, 7.0 mmol) and N.N-dimethylformamide (20 m.), at 0°C, and then the reaction mixture was stirred for 40 mixtures at room temperature. The tributyl-lodomethyl-tin (2.0 g, 4.6 mmol) described in Manufacturing Example 197-22 was added dropwise to the reaction mixture at 0°C, and then the reaction mixture was stirred ownight at room temperature. Heptane and water were added to the reaction mixture, and the organic layer was separated. The organic layer was washed and saturated aqueous addium-choride, and was concentrated under a reduced pressure. The reactious was purified by allica gel column chromatography (heptane: ethyl acetate = 20:1) to obtain the title compound (1.8 g, 6%).

¹H- MMR Spectrum (CDCl₃) δ (ppm): 0.81-0.98 (15H, m), 1.26-1.35 (6H, m), 1.43-1.57 (7H, m), 1.65-1.70 (1 H, m), 1.80-1.87 (2H, m), 2.14-2.21 (2H, m), 3.57 (2H, dd, J = 7.3, 7.0 Hz), 3.68-3.76 (1 H, m).

[Manufacturing Example 197-1-2] Potassium cyclobutoxymethyl trifluoroborate

[1514]

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O BFaK

[1515] To a mixture of tributyl-cyclobutoxymethyl-tin (1.0 g, 2.7 mmol) described in. Manufacturing Exemple 197-1-1 and identylydrofuran (10 mL) was added n-butyl lithium (1.5 M n-hexane solution, 1.7 mL, 2.7 mmol/dropwise at -78°C, and then the reaction mixture was sirred for 60 minutes at the same temperature. A tetrahydrofuran (10 mL) solution of firlispropyl borate (0.80 mL, 3.5 mmol) was added dropwise at to this mixture at -78°C, and then the reaction mixture was attreed for 50 minutes at the same temperature. Putsate of the reaction mixture was stirred for 50 minutes at room temperature. Water (10 mL) was added dropwise to the compound at room temperature, and then the reaction mixture was stirred for further 50 minutes at two same temperature. The reaction mixture was concentrated under a reduced pressure. The residule thus obtained was washed with defryl ether. Acetone was added to this residue, which was filtered. The filtrate was concentrated under reduced pressure. The residule thus obtained was washed with defryl ether. Acetone was added to this residue, which was filtered. The filtrate was concentrated under reduced pressure.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.30-1.42 (1 H, m), 1.48-1.58 (1 H, m), 1.61-1.73 (2H, m), 1.99-2.08 (2H, m), 2.31 (2H, q, J = 5.6 Hz), 3.60 (1 H, quin, J = 6.8 Hz).

[1516] The starting material, tributyl-iodomethyl-tin, was synthesized as follows.

55 [Manufacturing Example 197-2-1] TributyIstannyl-methanol

[1517]

[1518] To a mixture of disopropylamine (&2 m.L, 0.44 mol) and tetrahydrofuran (1000 m.L) were added dropwelse nbulylithium (£ M n-hexane solution, 56 mL, 0.5 mol) and n-buylithium (1.6 M n-hexane solution, 56 mL, 0.15 mol) at .78*C, and then the reaction mixture was stirred for 50 minutes. To this mixture was added dropwise tribulytin hydride (100 mL, 0.37 mol) at .78*C, and then the reaction mixture was stirred for 50 minutes at 0°C. The reaction mixture was cooled to .78*C, after which paraformatelehyde (1.3 g. 0.15 mol) was added to the reaction mixture. The reaction mixture was stowly raised to room temperature, and then the reaction mixture was stowly raised to room temperature, and then the reaction mixture were added water, an ammonium chloride aqueus solution, and diethyl other, and the organic layer was separated. The organic layer was washed first with a saturated sodium hydrogenearbonate aqueous solution and then with saturated aqueous sodium chloride. The organic layer was separated, and was concentrated under a reduced pressure. The residue was purified by neutral silice gel column chromatography (heptane : diethyl ether = 4 :1) to obtain the title commonium (95 to .80°C).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 0.88-0.94 (15H, m), 1.27-1.36 (6H, m), 1.49-1.55 (6H, m), 4.02 (2H, dd, J = 1.8, 6.6 Hz).

[Manufacturing Example 197-2-2] Tributyl-iodomethyl-tin

25 [1519]

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| ✓ Sn

38 [1820] To a mixture of triphenylphosphine (70g, 0.27 mol) and tetrahydroturan (500 mL) was added dropwise a mixture of N-iodosucchimide (60 g, 0.27 mol) and tetrahydrofuran (500 mL), at 0°C, and then the reaction mixture was stirred for 30 minutes at 0°C. To this mixture was added dropwise tributylstamyl-methanol (71 g, 0.22 mol) described in Manufacturing Example 197-2-1 at 0°C, and then the reaction mixture was stirred for 20 minutes at 0°C. The reaction mixture was stirred for 20 minutes at 0°C. The reaction mixture was stirred overnight at room temperature. Delivity either and vater were added to the reaction mixture was stirred and the reaction mixture was stirred to send the reaction mixture. And the organic layer was separated. The organic layer was washed first with a saturated sodium thiosulfate aqueous solution and then with saturated aqueous solution chioride. The organic layer was separated, and was concentrated under a reduced pressure, Heptane (400 mL) was added to the residue and filtered. The solvent in the filtrate was evaporated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane) to obtain the filte compound (90 g, 94%).

⁴⁵ ¹H-NMR Spectrum (CDCl₃) δ (ppm): 0.91 (9H, t, J = 7.2 Hz), 0.96-1.00 (6H, m), 1.28-1.37 (6H, m), 1.49-1.56 (6H, m), 1.94 (2H, t, J = 8.9 Hz).

[Example 198] 3-(1-(6-Benzyloxy-pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-pyridin-2,6-diamine

50 [1521]

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[1522] To an N,N-dimethylformamide (5.0 ml.) solution of 3(1/H.pynazol-4.yl)-pyridine-2,6-diamine (30.0 mg. 0.171 mmol) described in Manufacturing Example 36-1-2 was added sodium hydride (7.52 mg. 0.188 mmol, 60% in oil) on an ioe bath (0°C), which was stirred for 30 minutes at room temperature. Thereafter, 2-benzyloxy-5-chloromethyl pyridine (59.9 mg. 0.257 mmol) described in Manufacturing Example 191-1-2 was added to the mixture, which was stirred for 30 minutes at room temperature. The reaction mixture was partitioned into eithyl acatela and water. The organic layer was washed with water and a saturated sodium chloride aqueous solution, and dried with anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The residue was purified by NH silica gel column chromatograph (eth) escatelate lo totain the title compound (2.74 mg. 43.9%).

1H-NMR Spectrum (DMSO-d₀) 8 (ppm): 5.09 (2H, brs), 5.26 (2H, s), 5.34 (2H, s), 5.44 (2H, brs), 5.77 (1 H, dt, J = 2.8, 8.0 Hz), 6.86 (1 H, dt, J = 2.0, 8.8 Hz), 7.14-7.16 (1 H, m), 7.29-7.44 (5H, m), 7.57 (1 H, dt, J = 2.0 Hz), 7.68-7.71 (1 H, m), 7.29-7.44 (5H, m), 7.94 (1 H, dt, J = 1.6 Hz), 8.17 (1 H, s).

[Example 199] 3-(1-(4-(Pyridin-2-ylmethoxy)-benzyl)-1H-pyrazol-4-yl)-pyridin-2,6-diamine

5 [1523]

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[1524] To an N,N-dimethylformamide (5.00 mL) solution of 3(1 H-pyrazol-4-yf)-pyridin-2.6-diemine (30.0 mg, 0.17 mmol) described in Manufacturing Example 38-1-2 was added sodium hydriod (7.52 mg, 0.188 mmol, 60% in oil) on an obe lath (10°C) under introgen atmosphere, which was stirred for 30 minutes at room temperature. Thereafter, 2:(4-chioromethyl-phenoxymethyl-pyridine (5.9 mg, 0.257 mmol) described in Example 192 was added to the above mixture, where was stirred for 30 minutes at room temperature. The reaction mixture was partitioned into eithyl accides and water at room temperature. The organic layer was washed with water and saturated aquous sodium horidoe and dried over antylvorus magnesium suitlae, and the solvent was exponented under a reduced pressure. The residue was purified by NH silica pel column chromatography (ethyl accitate : heptane = 2:1 — ethyl accidate) to obtain the title compound (11.5 mg, 18.1 %).

5 1H-NMR Spectrum (DMSO-q_b) 8 (ppm): 5.06 (2H, brs), 5.16 (2H, s), 5.21 (2H, s), 5.43(2H, brs), 5.77 (1 H, d, J = 8.0 Hz), 6.99 (2H, d, J = 8.8 Hz), 7.32-7.35 (1 H, m), 7.49 (1 H, d, J = 7.6 Hz), 7.55 (1 H, s), 7.80-7.84 (1 H, m), 7.90 (1 H, s), 8.55-8.57 (1 H, m).

[Example 200] 3-(1-(6-Phenoxy-pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-pyridin-2,6-diamine

[1525]

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[1526] To an N,N-dimetrylformamide (6,00 mL) solution of 2-(1 H-pyrazol-4-yl-pyridine-2-6-diamine (30.0 mg, 0.17 mmol) described in Manufacturing Example 36-1-2 was added sodium hydride (7.52 mg, 0.188 mmol, 60% in oil) on an ice bath (0°C) under nitrogen atmosphere, which was stirred for 10 minutes at room temperature. Thereafter, 5-chlorometryl-2-phenoxy-pyridine (69-9 mg, 0.273 mmol) described in Manufacturing Example 193-1-2 was added to the above mixture, which was stirred for 30 minutes at room temperature. The reaction mixture was partitioned into ethyl acetate and water at room temperature. The organic layer was washed with water and saturated aqueous sodium chloride and dired over anhydrous magnesium sulfate, and the solvent was evaporated under a reduced pressure. The rescitum was purified by MR bilica ead column chromatoromyth (ethyl excetate) to obtain the title comooud (15.4 mg, 25.2%).

 $\begin{array}{l} \text{H-NMR Spectrum (DMSO-d_{e}) } \delta \left(ppm \right) : 5.09 \left(2H, brs \right), 5.29 \left(2H, s \right), 5.44 \left(2H, brs \right), 5.77 \left(1 \, H, dd, J = 0.8, 8.0 \, Hz \right), 7.01 \left(1 \, H, d, J = 8.4 \, Hz \right), 7.107.23 \left(4H, m \right), 7.41 \left(2H, t, J = 7.6 \, Hz \right), 7.59 \left(1 \, H, s \right), 7.79 \left(1 \, H, dd, J = 2.0, 8.4 \, Hz \right), 7.96 \left(1 \, H, s \right), 8.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 7.96 \left(1 \, H, s \right), 8.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 7.96 \left(1 \, H, s \right), 8.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 7.96 \left(1 \, H, s \right), 8.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 8.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 8.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 8.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 8.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 8.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H, d, J = 2.8 \, Hz \right), 9.14 \left(1 \, H$

5 [Example 201] 3-(3-(4-Benzyloxy-benzyl)-isoxazol-5-yl)-pyridine

[1527]

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(1958). To a tetrahydrofuran (3 mL) solution of 3-ethynylydridine (50 mg, 0.485 mmol) and (4-benzyloxy-phenyl)-acetohydrofuroly chloride (214 mg), 0.776 mmol) described in Mentileaturing Example 1-13 was added triethylamine (270 μ L, 1.94 mmol), which was stirred for 2.5 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water and startated aqueous sodium chloride, dried over anlydrous magneseium sutflex, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 1 : 4 to 1 : 2) to obtain the title compound (80 mg, 448%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 4.02 (2H, s), 5.05 (2H, s), 5.37 (1H, s), 6.93-6.97 (2H, m), 7.19-7.22 (2H, m), 7.30-7.44 (6H, m), 8.04-8.06 (1 H, m), 8.63-8.65 (1 H, m), 8.95-8.96 (1H, m).

[Example 202] 3-(3-(4-(Pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridine

[1529]

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[1530] To a tetrahydrofuran (3 mJ) solution of 3-ethynybyridine (10 mg, 0.97 mmol) and (4-(pytdin-2-yloxyme-thyl)-pranyl-sostohydromiony chloride (429 mg, 0.156 mmol) described in Menufacturing Example 2-1-5 was added triethylamine (54.1 µL, 0.388 mmol), which was stirred for 2.5 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water and saturated aqueous sodium choride, dried over anhydrous magnesium suiffate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by Ni+ silica gel column chromatography (ethyl acetate: heptane = 1: 4 to 1: 2, then 1: 1) to otabin the title compound (8 mg, 24%).

1H-NMR Spectrum (CDC_L) δ (ppm): 4.09 (2H, s), 5.37 (2H, s), 6.38 (1 H, s), 6.79-6.81 (1 H, m), 6.87-6.90 (1 H, m), 7.31 (2H, d, J = 8.4 Hz), 7.37-7.40 (1 H, m), 7.45 (2H, d, J = 8.4 Hz), 7.56-7.61 (1 H, m), 8.02-8.05 (1H, m), 8.16-8.18 (1H, m), 8.69-6.89 (1H, m), 8.46-8.61 (H, m), 8.46-8.89 (1 H, m), 8.46-8.89 (1 H, m), 8.46-8.18 (1 H, m), 8.46-8.89 (1 H, m), 8.

[Example 203] 3-(3-(4-(Pyridin-2-vimethoxy)-benzyl)-isoxazol-5-yl)-pyridine

[1531]

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[1832] To a tetrahydrofuran (3 mL) solution of 3-ethynybyridine (50 mg, 0.485 mmol) and (4-(pyridin-2-yinetinoxy)-phenyl)-acelohydroximoyl choined (215 mg, 0.786 mmol) described in Maunitacturing Example 203-1-4 was added trietyl-amine (270 μ L, 1.94 mmol), which was stirred for 2.5 hours at room temperature. This mixture was partitioned into ethyl acetale and water. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium suitlea, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1: 4 to 1: 2, then 1: 1) to obtain the title compound (71 mg, 43%).

1H.-NMR Spectrum (CDCl₃) δ (ppm): 4.02 (2H, s), 5.20 (2H, s), 6.37 (1H, s), 7.47 (2H, d, J = 8.4 Hz), 7.20-7.24 (2H, m), 7.21 (1 H, d, J = 8.4 Hz), 7.37-7.40 (1 H, m), 7.51-7.53 (1 H, m), 7.69-7.73 (1 H, m), 8.02-8.05 (1 H, m), 8.59-8.66 (1 H, m), 8.59-8.96 (1 H,

[1533] The starting material, (4-(pyridin-2-ylmethoxy)-phenyl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 203-1-1] 4-(Pyridin-2-ylmethoxy)-benzaldehyde

[1534]

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[1535] To an N,N-dimethylfomamide (250 mL) solution of 4-hydroxybenzaldehyde (20 g, 164 mmol) and 2-picolyl chloride (27 g, 165 mmol) was added potessium carbonate (88 g, 492 mmol), which was stirred for 3 days at room temperature. This mixture was partitioned into eithyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound was not purified but used for the next reaction.

35 1H-NMR Spectrum (DMSO-d₆) δ (ppm); 5.31 (2H, s), 7.21-7.25 (2H, m), 7.35-7.39 (1 H, m), 7.53-7.55 (1 H, m), 7.83-7.90 (3H, m), 8.59-8.61 (1 H, m), 9.88 (1H,s).

[Manufacturing Example 203-1-2] 2-(4-((E)-Nitro-vinyl)-phenoxymethyl)-pyridine

(0 [1536]

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[1537] A mixture of 4-(pyridin-2-yinethoxy)-benzaldehyde (29 g, 136 mmol) described in Manufacturing Example 203-1-1, nitromethane (96.6 mL, 680 mmol), armonium acetate (21 g, 272 mmol), and acetic acid (300 mL) was stirred for 21 hours at 100°C. This mixture was cooled to room temperature and concentrated under a reduced pressure. The residue was partitioned into eithyl acetate and water. The organic layer was separated, washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (33.9 g, 97%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.27 (2H, s), 7.04-7.06 (2H, m), 7.25-7.28 (1H, m), 7.49-7.54 (4H, m), 7.72-7.76 (1H, m), 7.96-7.99 (1H, m), 8.62-8.63 (1H, m).

[Manufacturing Example 203-1-3] 2-(4-(2-Nitro-ethyl)-phenoxymethyl)-pyridine

[1538]

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[1539] To a solution of 2:(4-((£)-nitro-vinyl) phenoxymethyl)-pyridine (33.9 g, 132 mmol) described in Manufacturing Example 203-1-2 in acetic acid (34 ml.) and dimethyl sulfoxide (576 ml.) was sided sodium borohydride (7.59 g, 211 mmol) at room temperature while cooling appropriately. This inchure was sirred for 5 hours at room temperature. This mixture was pertitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the reduce was recrystallized from heptane and ethyl acetate to obtain the title compound (6.81 g, 20%).

11-NMR Spectrum (CDCL) 5 (ppm): 3.26-3.30 (2H, m), 4.57-4.61 (2H, m), 5.51 (2H, s), 6.97 (2H, d, J = 8.8 Hz), 7.17 (2H, d, J = 8.8 Hz), 7.18 (2H, d,

Manufacturing Example 203-1-4] (4-(Pyridin-2-ylmethoxy)-phenyl)-acetohydroximoyl chloride

[1540]

[1541] To a methanol (36 mL) solution of 2-(4-(2-hitro-ethyl)-phenoxymethyl)-pyridine (3 g. 11.6 m/mol) described in Manufacturing Example 203-1-3 was added lithium methods (88 fl mg 23.2 m/mol), and this mixture was sirred at room temperature for 1 hour. The mixture was concentrated under a reduced pressure, water in the residue was agreed policy distilled with foliutene, and that residue was diluted with methylene chloride (46 mL) and tetrahydrofuran (23 mL). The mixture was cooled to -78°C, after which tilanium (IV) tetrachloride (4.08 mL, 37.1 m/mol) was added dropwise to this auspension. The mixture was stirred for 1 hour at room temperature. This mixture was cooled to -78°C and partitioned into ethyl acetate and water. The thin organic layer was separated, whethed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.98 g).

[1542] This compound was used in the following reaction without any further purification.

[Example 204] 3-(3-(2-Fluoro-4-(pyridi n-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1543]

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[1544] To a tetrahydrofuran (3 mL) solution of the 3-ethynyl-pyrdin-2-ylamine (38.4 mg, 0.325 mmol) discribed in Manufacturing Example 1-2-3 and (2-fluor-4-d-(ydin-2-yloxynethy-)-phenyl) acetolydroxinoylcholiotie (15 mg, 0.509 mmol) described in Manufacturing Example 204-1-8 was added triethylamine (97.2 µL, 0.697 mmol), which was stirred for 2 hours at 60°C. The midsture was cooled to room temperature and partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl scatae: heaten = 1 ± 4 to 1 : 2, then 1 : 1) to obtain the title compound (46 mp. 24%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 4.09 (2H, s), 5.37 (2H, s), 5.43 (2H, brs), 6.32 (1H, s), 6.70-6.73 (1 H, m), 6.80-6.82 (1 H, m), 6.88-6.92 (1 H, m), 7.19-7.30 (3H, m), 7.58-7.62 (1 H, m), 7.70-7.73 (1 H, m), 8.13-8.18 (2H, m).

[1545] The starting material, (2-fluoro-4-(pyridin-2-yloxymethyl)-phenyl) acetohydroximoyl chloride, was synthesized as follows

[Manufacturing Example 204-1-1] 2-(4-Bromo-2-fluoro-phenyl)-[1,3]dioxolane

[1546]

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[1547] A mixture of 4-bromo-2-fluorobenzaldehyde (10 g. 49.3 mmol), ethylene glycol (27.5 mL, 49.3 mmol), camphorsullonic acid (115 mg, 0.493 mmol), and toluene (250 mL) was stirred for 5 hours under reflux. The mixture was cooled to room temperature and a saturated sodium hydrogenarbonate aqueous solution was added thereto. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (12.5 g). The title compound was used in the following reaction without any further purification.

25 ¹H-NMR Spectrum (CDCl₃) 8 (ppm): 4.03-4.09 (2H, m), 4.10-4.16 (2H,m), 6.03 (1 H, s), 7.25-7.28 (1 H, m), 7.30-7.32 (1 H, m), 7.40-7.44 (1 H, m).

[Manufacturing Example 204-1-2] 4-[1,3]Dioxolan 2-vi-3-fluoro-benzaldehyde

[1548]

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[1548] To a tetrahydroluran (600 mL) solution of 2:(4-bromo-2-fluoro-phenyl-[1,3]dioxolane (12.5 g, 5.0.7 mmo) described in Manufacturing Example 2041-1 was added dropwise n-budyl lithium (28.5 mL, 2.67 M hexane solution, 7.6.1 mmol) over 15 minute. The mixture was stirred for 5 minutes at 78°C, after which a THF solution of N-formylmorpholine (5.61 mL, 55.8 mmol) was added to this reaction solution, which was stirred for another 2.5 hours at room temperature. Water and ethyl acetate were added to this mixture, which was partitioned. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (9.99 g). The title compound was used in the following reaction without any further purification.

[Manufacturing Example 204-1-3] (4-[1,3]Dioxolan-2-yl-3-fluoro-phenyl)-methanol

0 [1550]

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[1551] To a methanol solution (200 mL) of 4-[1,3]dioxolan-2-yl-3-fluoro-benzaldehyde (10 q, 50.9 mmol) described in

Manufacturing Example 204-1.2 was added sodium borohydride (2.12 g, 56 mmol), which was stirred for 1 hour at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnicisum sultate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:1) to obtain the title compount (2.44 o. 245).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.80 (1H, brs), 4.03-4.17 (4H, m), 6.21 (2H, d, J = 6.0 Hz), 6.08 (1 H, s), 7.09-7.19 (1 H, m), 7.38-7.54 (2H, m).

[Manufacturing Example 204-1-4] 2-(4-[1,3]Dioxolan-2-yl-3-fluoro-benzyloxy)-pyridine

[1552]

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[1553] To an N.N-dimetrylformamide solution (20 m.), of (41,3)dioxolan-2y/3-fluoro-phenyl)-methanol (2.44 g, 1.23 mno) described in Manufacturing Example 204-13 was added sodium hydride (537 mg, 1.48 mmol, 60% in oil), which was cooled to 0°C, after which 2-fluoropyridine (1.27 mL, 14.8 mmol, 90% and 60% in oil), which was stirred for 2 hours at 60°C. The mixture was cooled to room temperature and partitioned into ethyl acetzée and water. The organic layer was separated, washed with water, ridd over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gelcolumn chromatography (ethyl acetate : hextane = 1: 41 to obtain the title compound (2.17 of. 64%).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 4.05-4.17 (4H, m), 5.38 (2H, s), 6.09 (1 H, s), 6.79-6.83 (1 H, m), 6.88-6.91 (1 H, m), 7.16-7.25 (2H, m), 7.50-7.54 (1 H, m), 7.56-7.62 (1 H, m), 8.14-8.16 (1 H, m).

[Manufacturing Example 204-1-5] 2-Fluoro-4-(pyridin-2-yloxymethyl)-benzaldehyde

[1554]

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40 1555] To a solution of 2:44-[1,3]disoolan-2-yi-3-fluoro-benzyloxy)-pyridine (2.17 g. 7.88 mmol) described in Manufacturing Example 204-1-4 in methanol (10 mL) and tetrahydrofuran (10 mL) was added 5 N hydrochloric acid (8.43 mmol). This solution was stirred or 15 minutes at room temperature. This mixture was cooled to 0°C and neutralized with a saturated sodium hydrogencarbonate aqueous solution, after which it was extracted with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The fittrate was conditioned and the reduced pressure to obtain the title compound (1.81 g). The title compound was used in the following reaction without any further purification.

1H-NMR Spectrum (CDCl₈) δ (ppm):5.46 (2H, s), 6.82-6.94 (3H, m), 7.29-7.34 (1 H, m), 7.59-7.65(1 H, m), 7.85-7.89(1 H, m), 8.14-8.17(1H, m), 10.35 (1 H, s).

50 [Manufacturing Example 204-1-6] 2-(3-Fluoro-4-(E)-2-nitro-vinyl)-benzyloxy)-pyridine

[1556]

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[1557] A mixture of 2-fluoro-4-(pyridin-2-yloxymethyr)-benzaldehyde (1.81 g 7.81 mmol) described in Manufacturing of Example 2-oxt-5, nitroventhene (2.12 mt, 9.81 mmol), amonatum acetale (1.2 g 1.65 mmol), and scele caid (20 mt.) was stirred for 5 hours at 100°C. This mixture was cooled to room temperature and concentrated under a reduced pressure. The residue was partitioned rinte of thy scattle and water. The organic layer was separated, wheshed with vater, dried over anhydrous magnesium sulfate, and filtered. The residue was purified by silica gel column chromatography (ethn) acetate: i rebatae = 1 × 9 to botain the title compound (980 mt. 46%).

⁵ H. NMR Spectrum (CDCl₃) § (ppm): 5.44 (2H, s), 6.84-6.87 (1 H, s), 6.91-6.94 (1H, m), 7.24-7.32 (3H, m), 7.48-7.52 (1H, m), 7.61-7.65 (1 H, m), 7.71-7.75 (1 H, m), 8.14-8.16 (1H, m).

[Manufacturing Example 204-1-7] 2-(3-Fluoro-4-(2-nitro-ethyl)-benzyloxy)-pyridine

20 [1558]

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[1559] To a solution of 2-(3-fluoro-4-(f)-2-nitro-viny)-berrayloxy)-pyridine (980 m.g., 3.57 mmol) described in Manufacturing Example 204-1-6 in acetic acid (1 ml.) and dimethyl sulfoxide (17 ml.) was added sodium borohydride (203 mg. 5.36 mmol) at roomtemperature while cooling appropriately. This mixture was satirred for 3 hours at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (690 mg).

5 1H-NMR Spectrum (CDCl₃) 8 (ppm): 3.34-3.39 (2H, m), 4.60-4.67 (2H, m), 5.36 (2H, s), 6.80-6.83 (1 H, m), 6.89-6.92 (1 H, m), 7.17-7.21 (3H, m), 7.58-7.62 (1H, m), 8.15-8.17 (1 H, m).

[Manufacturing Example 204-1-8] (2-Fluoro-4-(pyridin-2-yloxymethyl)-phenyl) acetohydroximoyl chloride

0 [1560]

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[1561] To a methanol (20 mL) solution of 2-(3-fluoro-4-(2-nitro-ethyl)-benzyloxy)-pyridine (960 mg, 3.47 mmol) described in Manufacturing Example 204-1-7 was added lithium methoxide (264 mg, 6.94 mmol), and this mixture was stirred at room temperature for 1 hour. The mixture was concentrated under a reduced pressure, water in the residue was azooropically distilled with boluene, of that residue was diluted with methylene chloride (16 mL), 1 mmoly was added dropwise for mL). The mixture was cooled to 76°C, after which litamium ((v) letrachiode (1.22 mL, 11, 11 mmol) was added dropwise to this suspension. The mixture was stirred for 2 hours at 0°C. This mixture was cooled to -78°C and partitioned into ethyl accetate and water. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous macroseium sulfate, and filtered. The filter was concentrated under a reduced pressure to obtain the title compound (890 mg). The title compound was used in the following reaction without any further purification.

[Example 205] 3-(3-(4-Benzylsulfanyl-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1562]

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[1563] To a tetrahytrofruran (3 mL) solution of 3-ethynyi-pyridin-2-ylamine (50 mg, 0.423 mmol) described in Manufacturing Example 1-2-3 and (4-phenylsulfanylmethyl-phenyl) acetohydroximoyl chloride (197 mg, 0.677 mmol) described in Manufacturing Example 205-1-6 was added triethylamine (147 µL, 1.06 mmol), which was stirred for 18 hours at room temperature. This mixture was cooled to room temperature and partitioned into ethyl acetate and water. The organic layer was separated, weshed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH-silica gel column chromatography (ethyl acetate : heptane = 1 x to 1 x 21) to shift in the tille compound (29 mg, 1894).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.98 (2H, s), 4.11 (2H, s), 5.38 (2H, brs), 6.22(1 H, s), 6.70-6.73 (1 H, m), 7.16-7.18 (2H, m), 7.22-7.31 (7H, m), 7.69-7.71 (1 H, m), 8.14-8.15 (1H, m).

[1564] The starting material, (4-benzylphenylsulfanyl-phenyl) acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 205-1-1] 2-(4-Benzylsulfanyl-phenyl)-[1.3]dioxolane

[1565]

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38 [1868] To a tetralydrofuvar (100 mL) solution of 2-(4-bromopheny)-1,3-dioxane (5 g, 0.677 mmol) was added n-butyl lithium (14.9 mL, 2.64 M hexane solution, 39.2 mmol) at -78°C, which was stirred for 15 minutes. Benzyl disulfide (5.91 g, 24 mmol) was added dropwise to the reaction mixture at -78°C, which was stirred for 5 hours. The mixture was raised to 0°C and partitioned into ethyl scetate and water. The organic layer was separated, washed with saturated equeous sodium chloride, dried over anhydrous magnesim usuffate, and filtered. The fifting was concentrated under a reduced of pressure, and the residue was purified by sitica gel column chromatography (ethyl acetate : heptane = 1 : 4) to obtain the title compound (1.06 a. 18%).

1H-NMR Spectrum (DMSO-d_s) δ (ppm): 3.90-4.04 (4H,m), 4.26 (2H, s), 5.67 (1 H, s), 7.23-7.37 (9H, m).

[Manufacturing Example 205-1-2] 4-Benzylsulfanyl-benzaldehyde

[1567]

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[1568] To a solution of 2 (4-benzylsulfanyl-phenyl)-[1,3]dioxolane (1,06 g, 3.89 mmol) described in Manufacturing Example 205-1-1 in methanol (5 mt.) and tetrahydrofuran (5 mt.) was added 1 N hydrochloric acid (4.16 mt.), which was stried for 30 minutes at room temperature. The mixture was cooled to 0°C and neutralized with a saturated sodium hydrogencarbonate aqueous solution, and then extracted with ethyl acetate. The organic layer was separated, washed with water, dried over analydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the tilt compound (460 mg). The filte compound was used in the following reaction without any further purification

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 4.40 (2H, s), 7.26-7.28 (1H,m), 7.31-7.35 (2H, m), 7.43-7.45 (2H, m), 7.51-7.53 (2H, m), 7.79-7.81 (2H, m), 9.90 (1 H, s).

5 [Manufacturing Example 205-1-3] 1-Benzylsulfanyl-4-((E)-2-nitro-vinyl)-benzene

[1569]

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15 [1570] A mixture of 14-benzylsulfanyl-benzaldshyde (840 mg 3.68 mmo)) described in Manufacturing Example 206-1-2, nibromethane (997 µL, 18.4 mmol), ammonium acetate (567 mg, 7.36 mmol), and acetic acid (10 mL) was stirred for 2 hours at 100°C. This mixture was cooled to norm temperature and concentrated under reduced pressure. The residue was partitioned into ethyl acetate and water. The organic layer was esparated, washed with water and saturated aqueous coolfum chloride, dried over anhydrous magnesimu sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (950 mg). The title compound was used in the following reaction without any further purification.

<sup>1</sup>H-NMR Spectrum (DMSO- $d_0$ )  $\delta$  (ppm): 4.37 (2H, s), 7.23-7.34 (3H, m), 7.40-7.45 (4H, m), 7.76-7.81 (2H, m), 8.08 (1 H, d, J = 14 Hz), 8.20 (1 H, d, J = 14 Hz).

25 [Manufacturing Example 205-1-4] 1-Benzylsulfanyl-4-(2-nitro-ethyl)-benzene

[1571]

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38 [1572] To a solution of 1-benzy|sulfanyl-4-([6]-2-nitro-winyl-benzene (§65 nrg, 3.5 mmor)) described in Manufacturing Example 205-1-3 in acetic acid (0.6 mL) and dimethyl sulfoxide (10 mL) was added sodium borohydride (212 mg, 5.8 mmor)) while the internal temperature was held at 30°C or lower, which was stirred for 30 minutes at room temperature. The mixture was cooled with loe water, water was added, which was stirred for another 30 minutes. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (938 mg). The title compound was used in the following reaction without any further purification.

11-NNM Secturin (DMS-0-2, 6 (ppm): 3.15-3.18 (2H, m), 2.41 g.), 4.3.46.43 g.H, m), 7.18-7.35 (9H, m).

[Manufacturing Example 205-1-5] (4-Benzylphenylsulfanyl-phenyl) acetohydroximoyl chloride

[1573]

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[1574] To a methanol solution (12 ml.) of 1-benzyksulfanyl-4/2-nltro-ethyl-benzene (936 mg, 3.42 mmol) described in Manufacturing Example 205-1-4 was added lithium methoxide (260 mg, 6.84 mmol), which was stirred for 10 minutes at room temperature. The mixture was concentrated under a reduced pressure, water in the residue was azeotropically

distilled with toluene, and that residue was dituted with methylene chloride (16 mL) and tetrahylorfuran (8 mL). The system was cooled to - 78°C, after which tittanium (N) tetrachloride (825 µL, 7.52 mmol) was added dropwise to this suspension. The mixture was stirred for 1 hour at 0°C. This mixture was cooled to -78°C and partitioned into entry la pataset and water. The organic layer was separated, washed with saturated equeues sodium chloride, dried over anhydrous magnesium sultite, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.01 g). The title compound was used in the following reaction without any further purification.

[Example 206] 3-(3-(4-Phenylsulfanylmethyl-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1575]

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[1576] To a tetrahydrofuran (3 mL) solution of 3-ethynyl-pyridin-2-ylemine (50 mg, 0.423 mmb) described in Manufacturing Exemple 1-2-3 and (4-phenylsulfanylmethyl-phenyl) acetohydroximoy(chloride (197 mg, 0.677 mmb)) described in Manufacturing Exemple 2061-16 was added thethylemine (147 mL, 1.06 mmb), which was stirred for 18 hours at room 15 members of the mixture was cooled to room temperature and partitioned into ethyl acetate and water. The organic layer was separated, washed with water, divide over enhydrous megnesium sulfate, and filtered. The filtrate was concentrated under archiced propersion, and the residue was purified by NH ellica gel column chromatography (ethyl acetate : heptane = 1 : 4 to 1 : 2) to obtain the title compound (41 mg, 265).

<sup>1</sup>H-NMR Spectrum (CDCl<sub>3</sub>) δ (ppm): 4.03 (2H, s), 4.11 (2H, s), 5.42 (2H, brs), 6.23 (1 H, s), 6.69-6.73 (1 H, m), 7.16-7.35 (9H, m), 7.69-7.71 (1 H, m), 8.13-8.15 (1 H, m).

[1577] The starting material, (4-phenylsulfanylmethyl-phenyl) acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 206-1-1] 4-Phenylsulfanylmethyl-benzoic acid

5 [1578]

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[1579] A mixture of 4-(bromomethylibenzola eald (10 g. 46.5 mmol), sedium thipphenoxide (6.15 g. 45.5 mmol), and ethanol (100 mL) was stirred for 1.5 hours under reflux. This mixture was cooled to room temperature and acidified with 1 N hydrochloric acid. The precipitate thus produced was collected, dissolved in ethyl acetate, and washed with water. The organic layer was concentrated under a reduced pressure to obtain the title compound (10 g). The title compound was used in the following reaction without any further purification.

1H-NMR Spectrum (DMSO-d<sub>6</sub>) δ (ppm): 4.31 (2H, s), 7.16-7.20 (1H, m), 7.26-7.34 (4H, m), 7.45-7.47 (2H, m), 7.84-7.86 (2H, m), 12.9 (1 H, br.s).

(Manufacturing Example 206-1-2) (4-Phenylsulfanylmethyl-phenyl)-methanol

[1580]

[1881] To a suspension of lithium aluminum hydride (1.95, 6.13 mmol) in tetrahydrofuran (50 mL), was added dropwise a tetrahydrofuran solution of 4-phenylsuuflany/methyl-benzoic acid (5 g, 20.5 mmol) described in Manufacturing Exemple 206-1-1, which was stirred for 20 minutes at room temperature. This mixture was cooled with ice water, and water was carefully added. The mixture was filtered through a Cellie bed, and the filtrate was combined. The organic layer was separated, washed with water, dried over anhydrour snappeasims sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (2.01 g). The title compound was used in the following reaction without any further ourification.

1H-NMR Spectrum (DMSO-d<sub>E</sub>) δ (ppm): 4.22 (2H, s), 4.45 (2H, d, J = 5.6 Hz), 5.13 (1 H, t, J = 5.6 Hz), 7.16-7.34 (9H, m).

Manufacturing Example 206-1-3] 4-Phenylsulfanylmethyl-benzaldehyde

[1582]

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- 20 [1853] To a chloroform (10 mL) solution of (4-phenylsulfanylmethy-phenyl)-methanol (1 g, 4.34 mmo) described in Manufacturing Example 206-1-2 was added manganese dioxide (3.77 g, 43.4 mmo), which was stirred for 15 hours at room temperature. The manganese dioxide was removed with a Cellite bed, and the filtrate was concentrated under a reduced pressure to obtain the title compound (990 mg). The title compound was used in the following reaction without any further purification.
- 25 <sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>) & (ppm): 4.34 (2H, s), 7.16-7.20 (1 H, m), 7.27-7.35 (4H, m), 7.56 (2H, d, J = 8.0 Hz), 7.83 (2H, d, J = 8.0 Hz), 9.95 (1 H, s).

[Manufacturing Example 206-1-4] 1-((E)-2-Nitro-vinvl)-4-phenylsulfanylmethyl)-benzene

30 [1584]

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[1869] A mixture of 4-phenylsulfanylmethyl-benzaldehyde (990 mg, 4.34 mmol) described in Manufacturing Example 206-1-3, nitromethen (1.18 ml., 21.7 mmol), ammonium acetate (690 mg, 8.68 mmol), and acetic acid (6 mJ), was stirred for 6 hours at 100°C. This mixture was cooled to room temperature and partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.15 g). The title compound was used in the following reaction without any further purification.

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>) δ (ppm): 4.29 (2H, s), 7.16-7.20 (1H, m), 7.27-7.35 (4H, m), 7.44 (2H, d, J = 6.8 Hz), 7.77 (2H, d, J = 6.8 Hz), 8.08 (1H, d, J = 13.6 Hz), 8.18(1H, d, J = 13.6 Hz).

[Manufacturing Example 206-1-5] 1-(2-Nitro-ethyl)-4-phenylsulfanylmethyl-benzene

[1586]

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[1587] To a solution of 1-((E)-2-nitro-vinyl)-4-phenylsulfanylmethyl)-benzene (1.15 g, 4.24 mmol) described in Manufacturing Example 206-1-4 in acetic acid (0.6 mL) and dimethyl sulfoxide (10 mL) was added sodium borohydride (257

mg, 6.78 mmol), which was stirred for 30 minutes at room temperature. The mixture was cooled with ice water and partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.1.5 d). The title compound was used in the following reaction without any further outlification.

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>) δ (ppm): 3.17-3.20 (2H, m), 4.21 (2H, s), 4.80-4.84 (2H, m), 7.15-7.20 (3H, m), 7.27-7.33 (6H, m).

[Manufacturing Example 206-1-6] (4-Phenylsulfanylmethyl-phenyl) acetohydroximoyl chloride

[1588]

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[1899] To a methanol solution (12 mL) of 1-(2-nitro-ethyl)-4-phenylsulfanylmethylbenzene (1.1 g.4.08 mmol) described in Manufacturing Example 206-1-5 was added hitmum methoxide (366 mg, 8.06 mmol), which was stimed for 10 minutes at room temporature. The mixture was concentrated under a reduced pressure, water in the residue was azerdropically distilled with to leave, and that residue was added with methylene chloride (16 mL) and letrahydrofuran (8 mL). The system was cooled to -78°C, after which ittainum (10) tetrachoride (972 µL, 8.67 mmol) was added dropWise to this system was cooled to -78°C and partitioned into ethyl acetate and water. The organic layer was separated, washed with saturated aqueous sodium chloride, office dover anlydrous magneelum sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.15 g). The title compound was used in the following reaction whothust any further purification.

1H-NMR Spectrum (DMSO-d<sub>6</sub>) δ (ppm): 3.78 (2H, s), 4.23 (2H, s), 7.15-7.19 (3H, m), 7.27-7.34 (6H, m), 11.7 (1H, s).

[Example 207] 3-(3-(4-bromo-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1590]

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[1991] To a tetrahytorfuran (3 mL) solution of 3-ethynyl-pyridin-2-ylarinine (50 mg, 0.428 mmol) described in Manufacturing Example 1-2-3 and 4-bromopheny laceborydroximoyl-olhoide (188 mg), 6.77 mmol) described in Manufacturing Example 207-1-3 was added triethylamline (147  $\mu$ L, 1.06 mmol), which was stirred for 15 hours at room temperature. The mixture was partitioned into eithylaectate and water. The organic layer was separated, washed with water, dried over annytorius magnesium suitately, acetate and water. The organic layer was separated, washed with water, dried over annytorius magnesium suitately, acetate and the filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate : heptane = 1 : 41 o 1 : 2) to obtain the title compound (33 m, 24%).

<sup>1</sup>H-NMR Spectrum (CDCl<sub>3</sub>) δ (ppm): 4.02 (2H, s), 5.42 (2H, brs), 6.24 (1 H, s), 6.70-6.74 (1 H, m), 7.16-7.18 (2H, m), 7.44-7.48 (2H, m), 7.70-7.72 (1 H, m), 8.14-8.16(1 H, m).

[1592] The starting material, 4-bromophenyl acetohydroximoyl chloride, was synthesized as follows.

55 [Manufacturing Example 207-1-1] 1-Bromo-4-((E)-2-nitro-vinyl)-benzene

[1593]

[1594] A mixture of 4-bromobenzaldehyde (16.8 g, 91 mmol), nitromethane (24.6 mL, 455 mmol), ammonium acetate (14.g, 182 mmol), and acetic acid (160 mL) was stirred for 4 hours at 100°C. This mixture was cooled to room temperature and poured into water. The precipitate thus produced was collected, washed with water, and dried under a reduced pressure to obtain the title compound (17.4 g). The title compound was used in the following reaction without any further nutrification.

 $^{1}$ H-NMR Spectrum (DMSO-dg) δ (ppm): 7.71 (2H, d, J = 8.4 Hz), 7.82 (2H, d, J = 8.4 Hz), 8.13(1 H, d, J = 13.6 Hz), 8.27 (1 H, d, J = 13.6 Hz).

[Manufacturing Example 207-1-2] 1-Bromo-4-(2-nitro-ethyl)-benzene

[1595]

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[1596] To a solution of 1-bromo-4-((E)-2-intro-vinyl)-benzene (1 g, 4.37 mmol) described in Manufacturing Example 207-1-1 in acetic acid (0.6 mL) and directly is sulfoxide (10 mL) was added sodium borehydride (265 mg, 6.99 mm) which was stirred for 30 minutes at room temperature. The mixture was cooled with io evitare and partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (948 mg). The title compound was used in the following reaction without any further ourification.

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>)  $\delta$  (ppm): 3.20 (2H, t, J = 6.8 Hz), 4.85 (2H, t, J = 6.8 Hz), 7.25 (2H, d, J = 8.2 Hz), 7.51 (2H, d, J = 8.2 Hz).

[Manufacturing Example 207-1-3] 4-Bromophenyl acetohydroximoyl chloride

[1597]

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[1598] To a methanol solution (12 mL) of 1-bromo-4-(2-nitro-ethyl)-benzene (948 mg, 4.12 mmol) described in Maninacturing Example 207-1-2 was added lithium methoxide (313 mg, 8.24 mmol), which was stirred for 10 minutes at room temperature. The mixture was concentrated under a reduced pressure, water in the residue was eze-dropkially distilled with foluene, and that residue was diluted with methylene chloride (6 mL) and tetrahydrofuran (8 mL). The system was cooled to - 79°C, after which litainium (10) tetrachloride (994 µL, 9.06 mmol) was added droyles to this suspension. The mixture was stirred for 1 hour at 0°C. This mixture was cooled to -78°C and partitioned into ethyl acetate and water. The organic layer was esperated, washed with saturated aqueous sodium chioride, died over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (990 mg). The title compound was used in the following reaction without any further purification.

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>E</sub>) δ (ppm): 3.82 (2H, s), 7.23(2H, d, J = 8.4 Hz), 7.54 (2H, d, J = 8.4 Hz), 11.8 (1 H, s).

[Example 208] 3-(3-(5-(4-Fluoro-benzyl)-furan-2-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1599]

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[1800] To a tetrahydrofuran (a m.l.) solution of 3-ethynyl-pyridin-2-ylamine (50 mg, 0.423 mmol) described in Manutacturing Example 1-2-3 and (5-(4-fluorobenzyl)-furan-2-yl) acetohydroximoyl chloride (181 mg, 0.877 mmol) described in Manufacturing Example 2021-1-5 was added thethylamine (147 µL, 1.06 mmol), which was stirred for 19 hours at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sutflax, and filtered. The fittler was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:4 to 1:2) to obtain the title compound (9 mg, 6%).

¹H-NMR Spectrum (CDCb<sub>d</sub>) δ (ppm): 3.91 (2H, s), 4.04 (2H, s), 5.39 (2H, brs), 5.93 (1H, d, J = 3.0 Hz), 6.07 (1 H, d, J = 3.0 Hz), 6.07 (1 H, m), 5.96-7.01 (2H, m), 7.17-7.21 (2H, m), 7.66-7.68 (1 H, m), 8.15-8.17 (1 H, m).
[1601] The starting material, (5-4-fluoroberzyl)-furan-2-yl) ecotolydroximoyl chloride, was synthesized as follows:

[Manufacturing Example 208-1-1] 2-(5-(4-Fluoro-benzyl)-furan-2-yl)-[1,3]dioxolane

[1602]

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1803] To a tetrahydrotrum (60 m.) solution of 24 (1,3-dioxolan-2y-furan (5,3,85.7 mmol) was added n-bulyl lithium (15.8 m.L, 2.64 M hexane solution, 41.1 mmol) at -78°C, which was stirred for 1 hour at that temperature. A tetrahydrofurar solution of 4-fluoroberzyl bromide (6.9 g., 36.5 mmol) was added dropwise to this mixture, which was stirred for another hour at -78°C. The mixture was raised to room temperature and partitioned into ethyl acetate and a saturated ammonium chioride aqueous solution. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium suitate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate : heptane = 1:10 to 1:3) to obtain the title compound (45 g. 5.194).

 $^{1}$ H-NMR Spectrum (DMSO-d<sub>e</sub>)  $\delta$  (ppm): 3.86-3.90 (2H, m), 3.96-4.00 (4H, m), 5.78 (1 H, s), 6.07 (1 H, d, J = 3.0 Hz), 6.42 (1 H, d, J = 3.0 Hz), 7.12-7.16 (2H, m), 7.25-7.29 (2H, m).

[Example 208-1-2] 5-(4-Fluoro-benzyl)-furan-2-carbaldehyde

[1604]

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[1605] To a methanol (45 mL) solution of 2 (6:4-fluoro-benzyl)-furan-2-yl)-1/1,3(dioxolane (4.51 g, 18.2 mmo) described in Manufacturing Exemple 208-1-1 was added a solution (45 mL) of dutic acid (12.2 g, 63.7 mmo), which was vigorously stifred for 1 hour at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with a saturated sodium hydrogencarbonate aqueous solution, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (4.51 g, 51 %). The title compound was used in the following reaction without any further purification.  $^{1}$ H-NMR Spectrum (DMSO-d<sub>6</sub>) & (ppm): 4.11 (2H, s), 6.47-6.48 (1H, m), 7.15-7.19 (2H, m), 7.30-7.34 (2H, m), 7.47-7.48 (1 H, m), 9.49 (1 H, s).

[Manufacturing Example 208-1-3] 2-(4-Fluoro-benzyl)-5-((E)-2-nitro-vinyl)-furan

[1606]

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[1607] A mixture of 5-(4-fluoro-benzyl)-furan-2-carbaldehyde (1 g, 4.89 mmol) described in Manufacturing Example 2081-12, nitromethane (1.32 mi., 24.5 mmol), amnohum acetate (754 mg, 9.78 mmol), and acetic acid (10 mil), was stirred for 5 hours at 100°C. This mixture was cooled to room temperature and partitioned into ethyl acetale and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.21 g). The title compound was used in the following reaction without any further purification.

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>) & (ppm): 4.08 (2H, s), 6.42 (1 H, d, J = 3.4 Hz), 7.08-7.19 (2H, m), 7.22 (1 H, d, J = 3.4 Hz), 7.29-7.37 (2H, m), 7.64 (1H, d, J = 13.2 Hz), 7.96 (1H, d, J = 13.2 Hz).

[Manufacturing Example 208-1-4] 2-(4-Fluoro-benzyl)-5-(2-nitro-ethyl)-furan

5 [1608]

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[1609] To a solution of 2-(4-fluoro-benzyl)-5-((E)-2-nftro-vinyl)-furan (1.21 g, 4.89 mmol) described in Manufacturing Example 208-1-3 in acetic acid (0.6 mL) and dimethyl sulfoxide (10 mL) was added sodium borohydride (296 mg, 7.82 mmol), which was stirred for 30 minutes at room temperature. The mixture was cooled with ice water and partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (1.14 g). The title compound was used in the following reaction without any further purification.

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>e</sub>)  $\delta$  (ppm): 3.20-3.24 (2H, m), 3.91 (2H, s), 4.77-4.80 (2H, m), 6.00 (1 H, d, J = 3.0 Hz), 6.10 (1 H, d, J = 3.0 Hz), 7.08-7.15 (2H, m), 7.23-7.28 (2H, m).

[Manufacturing Example 208-1-5] (5-(4-Fluoro-benzyl)-furan-2-yl) acetohydroximoyl chloride

[1610]

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[1611] To a methanol solution (12 mL) of 2-(4-fluoro-beray)6-{2-nitro-ethyl}-furan (1.14 g. 4.57 mmol) described in Manufacturing Example 208-1-4 was added lithium methads (347 mg. 9.1 4 mmol), which was stirred for 10 minutes at room temperature. The mixture was concentrated under a reduced gressure, water in the residue was accorporately distilled with tolluene, and that residue was diffued with methylene chloride (15 mL) and tetrahydrofuran (8 mL). The system was cooled to -78°C, after which tiltanium (IV) tetrachioride (1.1 mL, 10.1 mmol) was added dropwise to this suspension. The mixture was stirred for 1 hour aft 0°C. This mixture was cooled to -78°C and partitioned into ethyl acetate

and water. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (940 mg). The title compound was used in the following reaction without any further purification.

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>)  $\delta$  (ppm): 3.82 (2H, s), 3.93 (2H, s), 6.03 (1H, d, J = 3.0 Hz), 6.20 (1 H, d, J = 3.0 Hz), 7.11-7.15 (2H, m), 7.23-7.27 (2H, m), 11.8 (1 H, s).

[Example 209] 3-(3-(4-(Pyridin-2-yloxy)-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1612]

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[1613] To a tetrahydrotruan (5 m.l.) solution of 3-ethynyl-pyridin-2ylamine (45 mg. 0.38 mmol) described in Manufacturing Example 12-3 and (4-(pyridin-2ylavy)barens-eactohydrotrony chloride (200 mg. 0.78 mmol) described in Manufacturing Example 209-1-4 was added triethylamine (158 mg. 1.4 mmol), which was etirred for 10 minutes at 60°C. The reaction solution was cooled for own temperature. NH silice get was added, and the solvent was evaporated under a reduced pressure. The crude product that hed adsorbed to the NH silice get was purified by NH silica get column chromatography (hepsane : ethw lacette = 2 t. 1.1 t.) to obtain the title compound (4d or n. 30°A).

1H-NMR Spectrum (DMSO-d<sub>a</sub>) δ (ppm): 4.05 (2H, s), 6.28 (2H, brs), 6.88-6.72 (1 H, m), 6.87 (1 H, s), 7.00-7.03 (1 H, m), 7.05-7.14 (3H, m), 7.37 (2H, d, J = 8.4 Hz), 7.81-87 (1 H, m), 7.87-7.91 (1 H, m), 8.08-8.11 (1 H, m), 8.11-8.14 (1 H, m). 11641 The starting material. (4-inviding-2-vjox)becapen-bacetohydroximov thoride, was swithesized as follows:

[Manufacturing Example 209-1-1] 4-(Pyridin-2-yloxy)-benzaldehyde

[1615]

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[1616] To an N,N-dimethyfformamide solution (100 mL) of 4-hydroxybenzaldehyde (10 g, 82 mmol) and 2-fluoropyridine (8.0 g, 82 mmol) was added sodium hydride (3.3 g, 82 mmol, 80% in oil), which was stirred for 30 milutes at 120°C, and he for 54 milutes at 140°C, and he for 26 hums at 160°C. The mixture was coolect nor memperature and partitioned into ethyl acetate and water. The organic layer was separated, washed with water (three times), and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate 4 x 110 to obtain the title compound (9.3 a. 57%).

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>8</sub>) δ (ppm): 7.15-7.20 (1H, m), 7.20-7.25 (1H, m), 7.33 (2H, d, J = 8.0 Hz), 7.40-8.00 (3H, m), 8.20-8.24 (1 H, m), 9.98 (1 H, s).

[Manufacturing Example 209-1-2] 2-(4-((E)-2-Nitro-vinyl)-phenoxy)-pyridine

[1617]

[1618] A mixture of 4-(pyridin-2-yloxy)-benzaldehyde (9.3 g, 47 mmol) described in Manufacturing Example 209-1-1, nitromethane (14 g, 230 mmol), ammonium acetate (11 g, 140 mmol), and acetic acid (50 mL) was stirred for 1 hour and 30 minutes at: 100°C. This mixture was cooled to room temperature, and water was added to precipitate a solid. The solid was filtered to obtain the title compound (9.9 g, 87%).

1H-NMR Spectrum (DMSO-dL) δ (ppm): 7.11-7.14 (1H. m), 7.18-7.25 (3H. m), 7.89-7.94 (3H. m), 8.13-8.24 (3H. m),

[Manufacturing Example 209-1-3] 2-(4-(2-Nitro-ethyl)-phenoxy)-pyridine

[1619]

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5 [1620] To a solution of 2-(4-((5)-2-nitro-vinyl)-phenoxy)-pyridine (9.9 g, 41 mmol) described in Manufacturing Example 209-1-2, acetic acid (2.5 g) and dimethyl sulfoxide (60 mL) was added sodium borohydride (770 mg, 20 mmol) while the temperature was held at 30°C or lower, which was stirred for 15 minutes at room temperature. This reaction solution was partitioned into eithyl acetate and water while the temperature was held at 30°C or lower. The organic layer was spararated and concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography (heptane; et My locatela = 31) to obtain the title compound (4.6 g, 45%).

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>) & (ppm): 3.24 (2H, t, J = 7.2 Hz), 4.87 (2H, t, J = 7.2 Hz), 6.99 -7.20 (1 H, m), 7.07 (2H, d, J = 8.0 Hz), 7.09-7.14 (1 H, m), 7.31 (2H, d, J = 8.0 Hz), 7.81-7.86 (1 H, m), 8.12-8.16 (1H, m).

[Manufacturing Example 209-1-4] (4-(Pyridin-2-yloxy)benzene)-acetohydroximoyl chloride .

[1621]

[1622] To a methanol solution (30 mL) of 2-(4-(2-nitro-ethyl)-phenoxy)-pyridine (2.0 g, 8.2 mmol) described in Manufacturing Example 209-1-3 was added lithium methoxide (470 mg, 12 mmol), and this mixture was concentrated under a reduced pressure. To luene was added to the residue, and the solvent was evaporated under a reduced pressure. To asolution of this residue in methylene chloride (40 mL) and stershydrofuran (20 mL) was added titanium (V) setrachioride (2.3 mL, 21 mmol) while sitting a 7-6°C. This suspension was sittered for 15 minutes at 0°C, and then for another 20 minutes at room temperature. The mixture was poured into ice water and stirred for 30 minutes. Ethyl scetate was added, and the organic layer was separated, washed with aqueous osubumichloride (one time), dired over anhydrous magnesium stafte, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (2.1 g, 98%). 11-MMR Spectrum (DMSO-d<sub>4</sub>) 8 (ppm): 3.44 (24, s), 7.01-7.05 (1H, m), 7.07-7.15 (3H, m), 7.29 (2H, d, J = 8.0 Hz), 7.82-7.88 (H, m), 8.13-8.16 (H, m), 11.75(H; hz), m., 11.75(H; hz), m., 11.75(H; hz), m., 11.75(H; hz).

Example 210] 3-(3-(6-Benzyl-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamine

[1623]

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[1624] A mixture of 3-othywyl-pyridin-2 ylamine (30 mg, 0.25 mmol) described in Manufacturing Example 1-2-3, 2-(6-benzyl-pyridin-3-yl)-actehydroximoyl chloride (88 mg, 0.34 mmol) described in Manufacturing Example 210-1-7, In-ethylamine (77 mg, 0.76 mmol), and tetrahydroturan (6 ml,) was stirred for 25 minutes at 50°C. This reaction solution was partitioned into ethyl acetate and water. The organic layer was separated and concentrated under a reduced pressure. The residue was purified by NH silics gel column chromatography (heptane: ethyl acetate = 2:1, 1:1, ethyl acetate) to both in the title compound (4.6 mg, 5.3%).

1H-NMR Spectrum (DMSO-d<sub>b</sub>) δ (ppm); 4.03 (2H, s), 4.06 (2H, s), 6.26 (2H, brs), 6.69 (1 H, dd, J = 4.8, 7.6 Hz), 6.84 (1 H, s), 7.15-7.22 (1 H, m), 7.22-7.30 (5H, m), 7.65 (1 H, dd, J = 2.0, 8.0 Hz), 7.86 (1 H, dd, J = 2.0, 8.0 Hz), 8.08 (1 H, dd, J = 4.4, BHz), 8.48 (1 H, d, J = 2.4 Hz), 8.48 (1 H, d, J = 2.4 Hz), 8.48 (1 Hz), 8.48 (1 H, d, J = 2.4 Hz), 8.48 (1 Hz

[1625] The starting material, (6-benzyl-pyridin-3-yl)-acetohydroximoyl chloride, was synthesized as follows.

[Manufacturing Example 210-1-1] 6-Bromo-pyridine-3-carbaldehyde

[1626]

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[1627] To a diethyl ether (500 mL) solution of 2,5-dibromopyridine (25 g, 110 mmol) was added dropwise n-butyl lithium (2.67 M n-haxane solution, 45 mL, 120 mmol) at .7°CC, which was stirred for 25 minutes. To this solution was added dropwise N,4-dimethylformamide (9.0 mL, 120 mmol) at .7°CC. Upon completion of this addition, the reaction solution was gradually cooled to room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane : ethyl scatetale = 8 : 1) to obtain the title compound (8.0 g, 41%).

1H-NMR Spectrum (DMSO-d<sub>n</sub>) δ (ppm): 7.89-7.92 (1H, m), 8.15-8.19 (1H, m), 8.89-8.92 (1 H, m), 10.09 (1 H, s).

[Manufacturing Example 210-1-2] 2-Bromo-5-[1,3]dioxolan-2-vI-pyridine

45 [1628]

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[1829] A mixture of 8-bromo-pyridine-3-carbatdehyde (8.0 g, 45 mmol) described in Marufacturing Example 210-1-1, ethylene glyco(6.5 g, 86 mmol), Potoleanselution, acid (820 mg, 4.5 mmol), and bulene (110 ml.) was stirred for 40 minutes under reflux. (The water produced in this reaction was removed with a Dean-Stark trap.) The reaction solution was concentrated under a reduced pressure, and the residue was partitioned into 4 five destite and water. The ornacion

layer was separated and passed through a glass filter provided with NH silica gel (eluted with ethyl acetate). The eluate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 8:11 to obtain the title compound (6.8 o. 5.9%).

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>) δ (ppm): 3.93-4.11 (4H, m), 5.84 (1 H, s), 7.68-7.72 (1 H, m), 7.77-7.82 (1 H, m), 8.44-8.47 (1H, m).

[Manufacturing Example 210-1-3] 2-Benzyl-5-[1,3]dioxolan-2-yl-pyridine

[1630]

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[1631] To a suspension of zinc (5.0 g. 77 mmol, highly rescribe Rieke metal, 100 mL tetrahydrofuran suspension) and tetrahydrofuran (300 mL) was added dropwise benzy bromide (7.9 mL, 66 mmol) at 0°C, which was stirred for 4 hours at the same temperature. To this suspension were added bis(triphenylphosphine) nickel (10) chloride (6.8 g. 8.8 mmol) and 2-bromo-5{1,3|dloxolan-2-yi-pyridine (11 g. 49 mmol) described in Manufacturing Example 210-12, which was stirred for another 2 hours at room temperature. The reaction solution was partitioned into ethyl sceletale and an ammonium chloride aqueous solution. The organic layer was separated and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane: ethyl acetate = 2:1, 1:1) to obtain the title compound (7.3 g. 62%).

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>) δ (ppm): 3.92-4.06 (4H, m), 4.10 (2H, s), 5.78 (1H, s), 7.16-7.22 (1 H, m), 7.25-7.32 (5H, m), 7.74 (1H, dd, J = 2.0, 8.0 Hz), 8.55 (1H, d, J = 2.0 Hz).

[Manufacturing Example 210-1-4] 6-Benzyl-pyridine-3-carbaldehyde

[1632]

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[1633] 2-8enzy6-51,3(dioxolan-2-yt-yyrdine (7.3 g, 30 mmol) described in Manufacturing Example 210-1-3 and 2 N hydrochloric acid (100 mL) were stirred for 15 minutes at 100°C. The reaction solution was cooled to room temperature and partitioned into stryl acetate and a 5 N sodium hydroxide solution (40 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (4.7 g, 79%).

1H-NMR Spectrum (DMSO- $d_0$ )  $\delta$  (ppm): 4.20 (2H, s), 7.18-7.25 (1H, m), 7.26-7.32 (4H, m), 7.50 (1 H, d, J = 8.0 Hz), 8.16 (1 H, dd, J = 2.0, 8.0 Hz), 8.97-9. 01 (1 H, m), 10.06 (1 H, s).

Manufacturing Example 210-1-5] 2-Benzyl-5-((E)-2-nitro-vinyl)-pyridine

[1634]

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[1635] A mixture of 6-benzyl-pyridine-3-carbaldehyde (4.7 g.24 mmol) described in Manufacturing Example 2 (0-1-4, nitromethane (7.3 g, 120 mmol), armonium acetate (6.6 g, 72 mmol), and acetic acid (40 mL) was stirred for 90 minutes at 100°C. The reaction solution was partitioned into ethyl acetate and water. The organic layer was washed with saturated aqueous sodium bicarbonate and concentrated under a reduced pressure. The residue was purified by silica gel column chromatopraphy (heptane: ethyl acetate = 2: 11 to obtain the title compound (1.2 g, 21 %).

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>g</sub>)  $\delta$  (ppm): 4.11 (2H, s), 7.14-7.21 (1 H, m), 7.23-7.29 (4H, m), 7.38 (1 H, d, J = 8.0 Hz), 8.12 (1 H, d, J = 13.6 Hz), 8.18 (1 H, dd, J = 2.0, 8.0 Hz), 8.26 (1H, d, J = 13.6 Hz), 8.87 (1 H, d, J = 2.0 Hz).

[Manufacturing Example 210-1-6] 2-Benzyl-5-(2-nitro-ethyl)-pyridine

[1636]

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[1637] To a mixture of 2-benzyl-5-((b)-2-nitro-winyl)-pyrdine (1.2 g, 5.0 mmol) described in Manufacturing Example 210-1-5, acetic acid (300 mg, 5.0 mmol), and dimethyl sulfoxide (10 mL) was added sodium borohydride (94 mg, 2.5 mmol), which was stirred for 10 minutes at room temperature. The reaction solution was partitioned into ethyl acetate and water. The organic layer was separated and passed through a glass filter provided with NH silica gel (eluted with ethyl acetate). The elutate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (heptane: ethyl acetate = 2:1) to obtain the title compound (260 mg; 22%).

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>) δ (ppm): 3.19 (2H, t, J = 6.8 Hz), 4.04 (2H, s), 4.86 (2H, t, J = 6.8 Hz), 7.16-7.30 (6H, m), 7.62 (1H, dd, J = 2.4, 8.0 Hz), 8.39 (1 H, d, J = 2.4 Hz).

[Manufacturing Example 210-1-7] (6-Benzyl-pyridin-3-yl)-acetohydroximoyl chloride

[1638]

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[1639] To 2-benzyl-5-(2-nitro-ethyl)-pyridine (260 mg, 1.1 mmol) described in Manufacturing Example 210-1-6 and nethanol (5 ml.) was added time methode (8 n mg, 2.1 mmol), which was concentrated under a reduced pressure. Thanium(IV) tetrachloride (0.38 ml., 3.4 mmol) was added dropwise at -78°C to a suspension of the residue in methylene chloride (6 ml.) and tetralpyridrotran (2.5 ml.), which was stirred for 20 minutes at room temperature. This reaction solution was added to evaler and wateried with ethyl actates again (four times). The organic layers were combined, washed with equeous sodium chloride (one time), dired over annydrous magnesium suitles, and filtered. The littles was concentrated under a reduced pressure, and tetralpyforlors was added to the residue. The insolubles thus produced were filtered out. The filtrate was concentrated under a reduced pressure, and tetralpyforlors was added to the residue. The insolubles thus produced were filtered out. The filtrate was concentrated under a reduced pressure to obtain the title compound (180 mg, 63%).

 $^{1}$ H-NMR Spectrum (DMSO- $^{1}$ d<sub>e</sub>)  $\delta$  (ppm): 3.83 (2H, s), 4.07 (2H, s), 7.17-7.22 (1 H, m), 7.25-7.30 (5H, m), 7.60 (1 H, dd, J = 2.0, 8.0 Hz), 8.39 (1 H, d, J = 2.0 Hz), 11.77 (1 H, s).

[Example 211] 3-(3-(2-Fluoro-4-(pyridin-2-yloxymethyl)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1640]

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[1641] To a tetrahydrofuran (3 mL) solution of 3-ethynyl-pyridine-2,6-diamine (43.2 mg, 0.325 mmol) described in Manufacturing Example 13-1-3 and (2-fluoro-4-(pyridin-2-yloxymethyl-phenyl) acetohydroxhroyl chloride (150 mg, 0.509 mmol) described in Manufacturing Example 20-1-8 was added triethylamine (87.2 µL, 0.589 mmol) described in Manufacturing Example 20-1-8 was added triethylamine (87.2 µL, 0.589 mmol), which was stirred for 2 hours at room temperature. The mixture was partitioned into ethyl acetate and water. The organic layer was seperated, weaken dwt hwater and saturated squows soldium-chloride, died over anhydrous magnesium suifate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1: 1, then ethyl acetate) to obtain the title compound (73 mg, 37%).

1H-NIMR Spectrum (CDCls) & (pom): 4.05 (24; s), 4.49 (2H, hrs), 5.29 (2H, hrs), 5.37 (2H, s), 5.91-5.94 (1 H, m), 6.06

[Example 212] 3-(4-(5-(2,6-Diamino-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenoxymethyl)-benzonitrile

[1642]

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H<sub>2</sub>N NH<sub>2</sub>

[1643] To a methanol (3.3 mL) solution of 4-(5-(2,6-diamino-pyridin-3-yl)-isoxazol-3-ylmethy)-phenol (100 mg, 0.38 mmol) described in Manufacturing Example 18-1-1 was added a 2 N sodium hydroxide aqueous solution (108 µL, 0.38 mmol). This mixture was concentrated under a reduced pressure. N,N-dimethyflomamide (1.3 mL) and 3-bromomethyt-benzontrile (68 mg, 0.29 mmol) were added to the residue, which was stirred for 15 minutes at 60°C. This reaction solution was partitioned rinto eithy acetate and water. The organic layer was separated and concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 1: 2, then ethyl acetate) to both in the title compound (24 mg, 17%).

1H-MMR Spectrum (DMSO-d<sub>2</sub>) & (ppm); 3.88 (2H, s), 5.14 (2H, s), 5.79 (2H, brs), 5.82 (1 H, d, J = 8.4 Hz), 6.11 (2H, brs), 6.34 (1 H, s), 6.98 (2H, d, J = 8.4 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.50 (1 H, d, J 8.4 Hz), 7.61 (1 H, dd, J = 8.0, 8.0 Hz), 7.76.7 (2H, m), 7.91 (1H, s).

[Example 213] 3-(4-(5-(2.6-Diamino-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenoxymethyl)-benzoic acid methyl ester

[1644]

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[1645] The title compound (48 mg, 16%) was obtained according to the methods similar to those of Example 212, using 4(5-(2,6-diamino-pyridin-3-yl)-isoxazol-3-ylmethyl)-phenol (200 mg, 0.71 mmol) described in Manufacturing Example 18-1-1 and 3-bromomethyl-bezoic acid methyl ester (160 mg, 0.71 mmol).

5 1H-NMR Spectrum (DMSO-q<sub>1</sub>) δ (ppm): 3.86 (3H, s), 5.88 (2H, s), 5.77 (2H, s), 5.79 (2H, brs), 5.82 (1H, d, J = 8.4 Hz), 6.11 (2H, brs), 6.34 (1 H, s), 6.57 (2H, d, J = 8.4 Hz), 7.22 (2H, d, J = 8.4 Hz), 7.50 (1 H, d, J = 8.4 Hz), 7.55 (1 H, dd, J = 8.0 Hz), 7.71 (1 H, d, J = 8.0 Hz), 7.71 (1 H, d, J = 8.0 Hz), 7.71 (1 H, d, J = 8.0 Hz), 7.80 (1 H, d)

[Example 214] 3-(3-(4-(3-Ethynyl-benzyloxy)-benzyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[1646]

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[1647] To a tetrahydrofuran (10 mL) solution of 4-(5-(26-diamino-pyridin-3-yl)-isoxazol-3-ymethyl)-phenol (160 mg, 0.87 mmol) described in Manufacturing Example 18-1-1, (3-ethythyl-phenyl)-methanol (91 mg, 0.69 mmol) described in Manufacturing Example 214-1-2, and inphenylphosphine (180 mg, 0.69 mmol) was added diethyl azodicarboxylate (300 mg, 0.69 mmol) was added diethyl azodicarboxylate (300 mg, 0.69 mmol) was added otherly a column chart and adsorbed to the reaction solution, and the solvent was exposted under a reduced pressure. The crude product that had adsorbed to the NH silica gel was purified by NH silica gel column chromatography (heptane: ethyl acetate =2:1, then 1:1, then ethyl acetate 10 obtain the title compound (110 m, 5.1 %).

1H-NMR Spectrum (DMSO-d<sub>e</sub>) δ (ppm): 3.88 (2H, s), 4.20 (1 H, s), 5.09 (2H, s), 5.79 (2H, brs), 5.82 (1 H, d, J = 8.4 Hz), 6.10 (2H, brs), 6.34 (1 H, s), 6.96 (2H, d, J = 8.8 Hz), 7.22 (2H, d, J = 8.8 Hz), 7.38-7.54 (5H, m).

[1648] The starting material, (3-ethynyl-phenyl)-methanol, was synthesized as follows. [Manufacturing Example 214-1-1] 1-Bromo-3-methoxymethoxymethyl-benzene

[1649] To a tetrahydrofuran (100 mt) solution of 3-bromobenzyl alcohol (10g, 54 mmol) was added sodium hydride (2.3 g. 98 mmol, 60% in oil) at room temperature. Then, chloromethyl methyl ether (6.2 g, 64 mmol) was added to this suspension, which was sittred for 15 minutes at 60°C. This mixture was partitioned into ethyl acetate and water. The organic layer was separated and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (heptane : ethyl acetate = 8 : 1) to obtain the title compound (10 g, 85%).

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>g</sub>) δ (ppm): 3.30 (3H, s), 4.53 (2H, s), 4.66 (2H, s), 7.30-7.38 (2H, m), 7.47-7.51 (1 H, m), 7.54 (1 H, m).

[Manufacturing Example 214-1-2] (3-Ethynyl-phenyl)-methanol

[1650]

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[1651] To a mixture of 1 brome 3-methoxymethoxymethybenzene (3.0 g. 13 mmol) described in Manufacturing Example 214-11, intenthyslybiacel/piece (2.6 g. 26 mmol), Nordisopropethyslamine (3.4 g. 26 mmol), copper (j) edide (500 mg. 26 mmol), and 1-methyl-2-pyrrolidone (30 ml.) was added tetraksiqtinhenylphosphine)palladium (j) (1.5 g. 3 mmol), such 1-methyl-2-pyrrolidone (30 ml.) was added tetraksiqtinhenylphosphine)palladium (j) (1.5 g. 3 mmol), which was stirred for 15 minuface at 60°C. This mixture was partitioned into chip acetate and water. The organic layer was separated and concentrated under a reduced pressure. The residue was purified by elica gel column chromatography (heptane: e1thyl acetate a: 1) to obtain a mixture of (3-methoxymethoxymethyl-phenylethynyl)-timely-plane) grown grown genome (3.7 g. d methoxymethoxymethyl-phenylethynyl)-timely-siame). Tetrabutylammonium fluoride (2 ml., 1 M tetrahydrofuran solution) was added to a tetrahydrofuran (30 ml.) solution of this mixture, which was stirred for 15 minutes at troon temperature. The reaction solution was partitioned into ethyl acetate and water. The organic layer was separated and concentrated under a reduced pressure. The residue was purified by sisting gel column chromatography (heptane: ethyl acetate = 20: 1) to obtain 1-ethynyl-3-methoxymethoxymethyl-benzene (470 mg.). To a methanol (10 ml.) solution of this 1-ethynyl-3-methoxymethoxymethyl-benzene (470 mg.). To a methanol (10 ml.) solution of this 1-ethynyl-3-methoxymethyl-benzene (470 mg.). To a methanol (10 ml.) solution of this 1-ethynyl-3-methoxymethyl-benzene (470 mg.). To a methanol (10 ml.) solution of this 1-ethynyl-3-methoxymethyl-benzene (470 mg.). To a methanol (10 ml.) solution of this 1-ethynyl-3-methoxymethyl-benzene (470 mg.). 26 minutes (30 mg.) 26% (30 mg.) 26

1H-NMR Spectrum (DMSO-d<sub>6</sub>) δ (ppm): 4.15 (1H, s), 4.49 (2H, d, J = 6.0 Hz), 5.25 (1H, t, J = 6.0 Hz), 7.31-7.35 (3H, m), 7.40-7.42 (1 H, m).

[Example 215] 3-(3-(4-(6-Chloro-pyrazin-2-yloxy)-benzyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[1652]

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[1653] To a methanol (1.5 mL) solution of 4-(5-(2,6-daimine-pyridin-3-yl-)sioxazol-3-ymethyl-phenol (50 mg, 0.18 mnol) described in Manufacturing Example 18-1-1 was added a 2 N sodium hydroide solution (89 μL), which was concentrated under a reduced pressure. 2,6-Dichiotopyrazine (28 mg, 0.19 mmol) and NN-dimethyr/omamide (0.75 mL) were added to the residue, which was stirred for 10 minutes at 10°C. The reaction solution was partitioned into ethyl acetate and water. The organic layer was separated and concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (heptane: ethyl acetate = 1:1, then ethyl acetate) to obtain the title compound (47 mg, 67%).

1H-NMR Spectrum (DMSO-d<sub>6</sub>) δ (ppm): 4.01 (2H, s), 5.82 (2H, brs), 5.83 (1 H, d, J = 8.4 Hz), 6.12 (2H, brs), 6.44 (1 H, s), 7.21 (2H, d, J = 8.4 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.53 (1 H, d, J = 8.4 Hz), 8.50 (1 H, s), 8.53 (1 H, s)

[Example 216] 3-(3-(4-Benzylsulfanyl-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

5 [1654]

[1655] To a tetrahydrofuran (3 mL) solution of 3-ethrynl-phyridine-2,6-diamine (60 mg, 0.376 mmol) described in Manindacturing Example 13-13 and (4-bercy)herbiskullaryl-phenyl) acetohydroximory (boldride (176 mg, 0.602 mmol) described in Manufacturing Example 205-1-5 was added triethylamine (131 µL, 0.94 mmol), which was stirred for 2 hours at room temperature. This mixture was partitioned into ethyl acetatie and water. The organic layer was separated, washed with water and saturated aqueous sodium chirofue, died over anhydrous magnesium sultate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica get column chromatography (ethyl acetate: heptane = 1: 1, then ethyl acetate) to obtain the title compound (80 mg, 56%).

H-NMR Spectrum (CDCl<sub>3</sub>) δ (ppm): 3.97 (2H, s), 4.10 (2H, s), 4.47 (2H, brs), 5.25 (2H, br s), 5.92 (1 H, d, J = 8.2 Hz), 5.96 (1 H, s), 7.17 (2H, d, J = 8.8 Hz), 7.23-7.29 (7H, m), 7.47 (1 H, d, J = 8.2 Hz).

[Example 217] 3-(3-(4-Phenylsulfanylmethyl-benzyl)-isoxazol-5-yl)-pyridin-2.6-diamine

[1656]

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1657] To a tetrahydroturan (3 m.l.) solution of 3-ethynyl-pyridine-2, 6-diamine (50 mg, 0.376 mmol) described in Manufacturing Exemple 13-1-3 and (4-phenylsulfanyfmethy-phenyl) acetohydroximoyl chloride (176 mg, 0.602 mmol) described in Manufacturing Exemple 206-1-6 was acided triethylamine (131 µL, 0.94 mmol), which was stirred for 2 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water and abstrated aqueuso sodium chloride, died over anhydroxim sampassium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: heptane = 1:1, then ethyl acetate) to obtain the title compound (88 mg, 67%). HH-MMR Spectrum (CDCL) à (porm), 3 so (2H, s), 4.1 (12+, s), 4.46 (2H, brs), 5.52 (1 H, d, J = 8.4 Hz),

[Example 218] 3-(3-(4-(3-Methyl-2-but-2-enyloxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

5.97 (1 H, s), 7.18-7.32 (9H, m), 7.47 (1 H, d, J = 8.4 Hz).

[1658]

[1659] The title compound (15 mg, 23%) was obtained according to the methods similar to those of Example 212, using 4-(5-(2,6-diamino-pyridin-3-yf)-sboxazoi-3-yimethyl-phenol (60 mg, 0.18 mmol) described in Manufacturing Example 18-1-1 and 1-brono-3-methyl-but2-ene (82 mg, 0.21 mmol).

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>6</sub>)  $\delta$  (ppm): 1.69 (3H, s), 1.73 (3H, s), 3.87 (2H, s), 4.48 (2H, d, J = 6.4 Hz), 5.41 (1H, t, J = 6.4 Hz), 5.41 (1H, t,

= 6.4 Hz), 5.79 (2H, brs), 5.82 (1 H, d, J = 8.0 Hz), 6.10 (2H, brs), 6.34 (1 H, s), 6.86 (2H, d, J = 8.4 Hz), 7.19 (2H, d, J = 8.4 Hz), 7.50 (1H, d, J = 8.0 Hz).

[Example 219] 3-(3-(4-Prop-2-ynyloxy-benzyl)-isoxazol-5-yl)-pyridine-2,6-diamine

[1660]

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H,N NN<sub>1</sub>

[1661] The title compound (38 mg, 68%) was obtained according to the methods similar to those of Example 212, 2 using 4-(5-(2,6-diamino-pyridin-3-yi)-isoxazol-3-yimethyl)-phenol (50 mg, 0.18 mmol) described in Manufacturing Example 18-1-1 and propargy bromide (32 mg, 0.27 mmol).

<sup>1</sup>H - NMR Spectrum (DMSO-dg) δ (ppm): 3.54 (1 H, t, J = 2.0 Hz), 3.89 (2H, s), 4.76 (2H, d, J = 2.0 Hz), 5.79 (2H, brs), 5.82 (1 H, d, J = 8.4 Hz), 6.10 (2H, brs), 6.35 (1 H, s), 6.93 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 8.8 Hz), 7.51 (1 H, d, J = 8.4 Hz).

25 [Example 220] 3-(3-(4-Bromo-benzyl)-isoxazol-5-yl)-pyridine-2,6-diamine

[1662]

H<sub>N</sub>N NH<sub>3</sub>

[1663] To a tetrahydrofuran (3 mL) solution of 3-ethynyl-pyridine-2,6-diamine (50 mg, 0.376 mmo) described in Mandecturing Example 13-13 and 4-fromophenyl acetohydroximoyl-thoride (150 mg, 0.602 mmo) described in Manufacturing Example 207-1-3 was added triethylamine (131 µL, 0.94 mmol), which was stirred for 2 hours at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water and saturated aqueous sodium-cholinde, dired over analyticum snagnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by NH silfate gel column chromatography (eftyl acetate: heptane = 1:1, then eithy acetate) to both in the title compound (85 mg, 68%).

 $^{1}\text{H-NMR Spectrum (CDCl}_3) \, \delta \, (\text{ppm}) : 3.97 \, (2\text{H, s}), \, 4.48 \, (2\text{H, brs}), \, 5.26 \, (2\text{H, brs}), \, 5.92 \, (1\,\text{H, d}, \, \text{J} = 8.4\,\text{Hz}), \, 5.97 \, (1\,\text{H, s}), \, 7.15 - 7.13 \, (2\text{H, m}), \, 7.44 - 7.48 \, (2\text{H, m}), \, 7.48 \, (1\,\text{H, d}, \, \text{J} = 8.4\,\text{Hz}).$ 

[Example 221] 3-(3-(5-(4-Fluoro-benzyl)-furan-2-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1664]

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<sup>12</sup> [1865] To a tertalydroturan (3 m.l.) solution of 3-ethyny-pyridin-2,6-diamine (50 mg, 0.378 mmol) described in Man-ufacturing Example 13-1-3 and (6 (4-fluorobenzyl)-hran-2-yl) acetohydroximoyl chloride (161 mg, 0.802 mmol) described in Manufacturing Example 208-1-5 was added triethylamine (131 µL, 0.94 mmol), which was stirred for 19 hours at room temperature. This mitture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water and saturated aqueous sordium chloride, evided over analydrous magnesium suitafe, and filterac. The filtrate was of concentrated under a reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate: etherane = 1:1, then ethyl acetate) to obtain the title compound (45 mg, 33%).

<sup>1</sup>H-NMR Spectrum (CDCl<sub>3</sub>) δ (ppm): 3.91 (2H, s), 3.99 (2H, s), 4.49 (2H, brs), 5.25 (2H, brs), 5.92 (1 H, d, J = 2.8 Hz), 5.95 (1 H, d, J = 8.4 Hz), 6.04 (1 H, s), 6.06 (1 H, d, J = 2.8 Hz), 6.96-7.01 (2H, m), 7.17-7.21 (2H, m), 7.45 (1 H, d, J = 8.4 Hz).

[Example 222] 3-(3-(4-(Pyridin-2-yloxy)-benzyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1666]

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[1687] To a tetrahydrofuran (15 ml.) solution of 3-ethynyl-pyridin-2,6-diamine (45 mg, 0.34 mmol) desorbed in Manufacturing Example 13-13 and (4-(pyridin-2-yloxy)benzene)-acetohydroximoyl chlorida (300 mg, 1.1 mmol) described in Manufacturing Example 208-1-4 was added triethylamine (120 mg, 1.1 mmol), which was stirred for 10 minutes at 60°C. The reaction solution was cooled to room temperature, NH silica gel was added, and the solvent was evaporated under a reduced pressure. The crude product that had adsorbed to the NH silica gel was purified by NH silica gel outurn chromatography (heptane: ethyl acetate = 1: 1, then ethyl acetate) to obtain the title compound (57 mg, 14%).

11-14-MRR Spectrum (DMSO-d<sub>0</sub>) δ (ppm): 3.97 (2H, s), 5.82 (2H, bs), 5.84 (1H, d, J = 8.0 Hz), 6.11 (2H, brs), 6.42 (1H, s), 6.99-7.03 (1 H, m), 7.05-7.13 (3H, m), 7.34 (2H, d, J = 8.0 Hz), 7.53 (1 H, d, J = 8.0 Hz), 7.81-7.86 (1 H, m), 8.12-8.14 (1 H, m).

[Example 223] 3-(3-(6-Benzyl-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2,6-diamine

[1668]

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[1669] To a tetrahydrofuran (5 mL) solution of 3-ethynyl-pyridin-2.6-diamine (20 mg, 0.15 mmol) described in Manu-

facturing Example 13-1-3 and 2-(6-beruyl-prividin-3-yl)-acotolyydroximoyl-chloride (79 mg, 0.30 mmol) described in Manufacturing Example 210-1-7 was added triethylamine (46 mg, 0.45 mmol), which was stirred for 30 minutes at 50°C. The reaction solution was cooled to room temperature and partitioned into ethyl acotata and water. The organic layer was separated and concentrated under a reduced pressure. The residue was purified by NH silica gel column chromatography (chtyl acotate, then ethyl acotate, the methanol = 20°1) to obtain the title compound (43 mg, 80%).

<sup>1</sup>H-NMR Spectrum (DMSO-d<sub>g</sub>)  $\delta$  (ppm): 3.95 (2H, s), 4.05 (2H, s), 5.80 (2H, brs), 5.82 (1H, d, J = 8.8 Hz), 6.11 (2H, brs), 6.40 (1 H, s), 7.15-7.30 (6H, m), 7.50 (1H, d, J = 8.8 Hz), 7.62 (1 H, dd, J = 2.0, 8.0 Hz), 8.46 (1 H, d, J = 2.0 Hz).

[Example 224] 3-(3-(6-Benzyloxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-N6-methyl-pyridin-2,6-diamine

[1670]

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[1671] To a mixture of 3-(3-(6-benzyloxy-pyridin-3-y-methyl-sexazot-5-y)-pyridin-2-£-dramine (50 mg, 0.13 mmol) escribed in Example 25 and N,N-dimethylformamide (0.5 mL) were added a formatishyde aqueeus solution (14 mg, 0.17 mmol, content: 37%), epicoline-borane (17 mg, 0.16 mmol), and acetic acid (50 µL) at room temperature, which was attired overnight at the same temperature. A saturated aodium hydrogencarbonate aqueeus solution was added to the reaction mixture, which was extracted with entry acettac. The origanic layer was concentrated queeus sodium chloride and dried over anhydrous magnesium sultate, after which the organic layer was concentrated under a reduced pressure. The residue that solutianie was purified by reverse-phase high performance liquid chromatography (using an acetonitrile-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain a crude product, and then purified by silica gist him-layer chromatography (disthyl either, hexane = 2.1) to obtain the title compound (2.5 mg, 4.6 Hz), 1.4 = 4.8 Hz), 3.91 (2H, s), 5.83 (1H, d), 5.83 (1H, d), 4.9 = 4.8 Hz), 5.87 (2H, br.s), 6.80 (1H, d), 5.88 (1H, d), 5.88

[Example 225] 2-(6-Amino-5-(3-(6-benzyloxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamino)-ethanol

[1672]

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[1673] To a mixture of 3-(3-(6-benzyloxy-yyridin-3-yhrethyl)-isoxazol-5-yh-pyridin-2-6-diamine (40 m.g. 0.11 mmo), described in Example 25 and N.N-dimethylformamide (0.5 ml.) were 2-hydroxyacetaldehyde (7.7 mg. 0.13 mmo), α-picoline-borane (14 mg. 0.13 mmol), and acetic acid (40 μ.l.) at room temperature, which was stirred for 100 minutes at the same temperature. A saturated sodium hydrogencarbonate aqueous sodium low as added to the reaction mixture, which was extracted with entry acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over arrhydrous magnesium sulfate, after which the organic layer was concentrated under a reduced pressure. The residue thus obtained was purified by reverse phase high performance liquid chromatography (using an accestorities water mobile elace containin 0.1 % influioroacetic acid to obtain a crude evoduct, and then purified by NH silica cell

column chromatography (ethyl acetate: methanol = 50: 1) to obtain the title compound (4.5 mg, 10%).
11H-NMR Spectrum (DMSO-46) § (ppm): 331-3.34 (2H, m), 3.48-3.51 (2H, m), 3.91 (2H, s), 5.39 (2H, s), 5.39 (2H, br, s), 5.39 (1H, d, J = 8.6 Hz), 6.39 (1 H, s), 6.72 (1 H, br), 6.85 (1 H, d, J = 8.4 Hz), 7.29-7.33 (1 H, m), 7.35-7.39 (2H, m), 7.42-7.44 (2H, m), 7.50 (1H, d, J = 8.6 Hz), 7.66 (1 H, dd, J = 2.6, 8.6 Hz), 8.14 (1H, d, J = 2.0 Hz).

[Example 226] N-(6-Amino-5-(3-(6-benzyloxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-yl)-2-methoxy-acetamide

[1674]

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[1675] To a mixture of 3-64-6-benzyloxy-pyridin-3-y-inethyly-boxazo-6-y-ly-pyridin-2- $\varrho$ -diamine (40 mg, 0.11 mmo) described in Example 25 and dichloromethane (1 mL) were added triethylamine (22  $\mu$ L, 0.16 mmol) and methoxyacety chloride (15 mg, 0.14 mmol) at room temperature, which was stirred for 2 hours at the same temperature. The solids that precipitated in the reaction mixture were filtered out. Tetrahydrofuran was added to the solid thus obtained, and this mixture was filtered. The filtrate was concentrated under a reduced pressure to obtain the title compound (3.4 mg, 7%). 1H-NMR Spectrum (DMSO-d<sub>2</sub>)  $\delta$  (ppm): 3.37 (3H, m), 3.98 (2H, s), 4.05 (2H, s), 5.33.(2H, s), 6.23 (2H, br.)s, 6.73 (1 H, s), 6.86 (1H, d, J = 8.4 Hz), 7.297-333 (1 H, m), 7.397-7.44 (6H, m), 7.68 (1H, dd, J = 2.6, 8.4 Hz), 7.91 (1 H, d, J = 8.4 Hz), 8.16 (1 H, d, J = 2.4 Hz), 8.70 (1 H, br.) =

[Example 227] (6-Amino-5-(3-(6-benzyloxy-pyridin-3-ylmethyl)-isoxazol-5-yl)-pyridin-2-ylamino)-acetic acid ethyl ester

[1676]

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[1677] To a mixture of 3-(3-(6-benzy)oxy-yridin-3-y-thethyl-)-laoxazo(5-y)-p-yridin-2-6-diamine (40 mg. 0.11 mmo) described in Exemple 25 and N. Ardmethylformaniel (6.5 ml.) were added glyoxyfic acid eithly ester polymer forem (16 mg. 0.16 mmo), κ-picoline-borane (14 mg. 0.13 mmol), and acetic acid (40 μL), which was stirred overnight at the same temperature. A saturated sodium hydrogenearbonate aqueous solution was added to the reaction mixture, which was corracted with eithyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium suiflate, after which the organic layer was concentrated under a reduced pressure. The residue thus obtained was purified by evereste-phase high performance liquid chromatography (using an acetoritire-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (4.9 mg. 8%) as a trifluoroacetic acid set. MS more (ES) 46.05 1 (MH\*)

[Example 228] (3-(3-(4-Benzyloxy-benzyl)-isoxazol-5-yl)-pyridin-2-yl)-dimethyl-amine

[1678]

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[1879] To a mixture of 3 (3 (4 benzyloxy-benzyl)-isoxazol-5-yl)-pyridin-2-ylamine (50 mg, 0.14 mmol) described in Example 1 and N,N-dimethylformamide (0.5 mL), were added a formaldehyde aqueous solution (34 mg, 0.42 mmol, content: 37%), α-picoline-borane (37 mg, 0.35 mmol), and acetic acid (50 μL), which was stirred overlight at the same temperature. Trifluoroacetic acid (50 μL) was added to the reaction mixture, which was stirred for 30 minutes at room temperature. The solvent was evaporated under a reduced pressure, and the residue thus obtained was purified by reverse-phase high performance liquid chromatography (using an acetonitria-water mobile phase containing 0.1 % trifluoroacetic acid) to obtain the title compound (15 mg, 21 %) as a trifluoroacetate.

[1680] The compounds (i) of the present invention or salts thereof exhibits excellent inhibition activity on the GPIanchored protein transport process based on the inhibition of fungal GPI biosynthesis, anti-Candida activity and anti-Aspergillus activity, and are also superior in terms of its physical properties, safety and metabolic stability, making it extremely useful as a preventive or therapeutic agent for fungal infections.

## [Pharmacological test examples]

[1681] In order to demonstrate the usefulness of the compounds (I) of the present invention, the antifungal activity of the compounds (I) of the present invention was measured by measuring 1; anti-Candida and anti-Aspergillus activity and 2; activity in the experimental systemic candidal infection model in mice.

30 1. Anti-Candida activity and anti-Aspergillus activity

## (1) Preparation of fungal suspension

[1682] For the C. albicans CAF2-1 strain, a fungal suspension from a standing culture for 48 hours at 30°C in a Sabouraud dextrose liquid culture medium (SDB) was diffued with RPM11640 medium to adjust a fungal suspension of 1.2 x 10° cells / mL. For the A. fumigatus Tsukuba strain, -80°C stored strain was diffued with RPMI 1840 medium to adjust to a fungal suspension of 4.5 x 10° cells / mL.

#### (2) Preparation of an agent dilution plate

[1863] Using a U-bottomed 96 well plate, 8 samples / plate (A to H) of sample dilution solutions were prepared. On the  $2^{\rm ml}$  to  $12^{\rm lm}$  rows were dispensed 10  $\mu$ L of dimethyl sulfoxide solution. Weighted sample was dissolved in dimethyl sulfoxide to prepare a 2.5 mg / mL solution,  $20 \mu$ L of this solution was added to the first row of the prepared plate, and 12 steps of two-foled step dilutions (10  $\mu$ L of solution + 10  $\mu$ L of dimethyl sulfoxide solution) were performed on the plate. This sample dilution solution was dispensed in the amount of 1  $\mu$ L to a flat-bottomed 96 well plate for MIC measurement to prepare a sample dilution plate.

## (3) Inoculation of fungal suspension and culture

[1684] The fungal suspension prepared in (1) was used in the amount of 99 µL / well to inoculate the flat-bottomed 96 well plate containing 1 µL / well of the test compound dilution prepared in (2), and a standing culture was carried out aerobically for 42-49 hours at 35°C.

## (4) MIC measurement

[1685] The minimum concentration that clearly inhibited fungal growth as compared to the control by visual inspection was determined as the minimum inhibitory concentration (MIC).

[1686] The following representative compounds prepared in the examples were measured for anti-Candida activity

and anti-Aspergillus activity by the measurement method described in 1. As a result, as shown in Tables 1 to 6, it was found that the compounds according to the present invention clearly had anti-Candida and anti-Aspergillus activity.

# TABLE 1

| 5  | Ex. No. | Anti-Candida<br>Activity (μg/mL) | Anti-Aspergillus<br>Activity (μg/mL) | Ex. No. | Anti-Candida<br>Activity (μg/mL) | Anti-Aspergillus<br>Activity (μg/mL) |
|----|---------|----------------------------------|--------------------------------------|---------|----------------------------------|--------------------------------------|
|    | 1       | 0.20                             | 0.20                                 | 21      | 1.56                             | 0.78                                 |
| 10 | 2       | 0.05                             | 0.20                                 | 22      | 0.20                             | 0.39                                 |
| 10 | 3       | 0.10                             | 0.78                                 | 23      | 0.78                             | 1.56                                 |
|    | 4       | 0.20                             | 0.39                                 | 24      | 0.39                             | 0.78                                 |
|    | 5       | 0.39                             | 0.39                                 | 25      | 0.20                             | 0.20                                 |
| 15 | 6       | 0.39                             | 0.39                                 | 26      | 0.78                             | 0.78                                 |
|    | 7       | 1.56                             | 0.20                                 | 27      | 0.20                             | 0.39                                 |
|    | 8       | 1.56                             | 0.78                                 | 28      | >25                              | 0.39                                 |
| 20 | 9       | 0.20                             | 0.39                                 | 29      | 0.39                             | 0.20                                 |
| 20 | 10      | 0.39                             | 0.78                                 | 30      | 0.10                             | 0.20                                 |
|    | 11      | 0.10                             | 0.39                                 | 31      | 0.20                             | 0.39                                 |
|    | 12      | 0.10                             | 0.10                                 | 32      | 0.20                             | 0.78                                 |
| 25 | 13      | 0.20                             | 0.10                                 | 33      | 0.39                             | 0.78                                 |
|    | 14      | 0.39                             | 0.39                                 | 34      | 0.78                             | 0.39                                 |
|    | 15      | 0.20                             | 0.39                                 | 35      | 0.20                             | 1.56                                 |
| 30 | 16      | 0.39                             | 0.39                                 | 36      | 0.39                             | 0.78                                 |
| 55 | 17      | 0.78                             | 0.20                                 | 37      | 0.39                             | 1.56                                 |
|    | 18      | 1.56                             | 0.78                                 | 38      | 0.78                             | 1.56                                 |
|    | 19      | 0.78                             | 0.39                                 | 39      | 3.13                             | 3.13                                 |
| 35 | 20      | 0.78                             | 0.20                                 | 40      | 0.39                             | 0.39                                 |

# TABLE 2

| 40 | Ex. No. | Anti-Candida<br>Activity (µg/mL) | Anti-Aspergillus<br>Activity (µg/mL) | Ex. No. | Anti-Candida<br>Activity (µg/mL) | Anti-Aspergillus<br>Activity (µg/ml) |
|----|---------|----------------------------------|--------------------------------------|---------|----------------------------------|--------------------------------------|
|    | 41      | 0.39                             | 0.20                                 | 61      | 0.20                             | 0.39                                 |
|    | 42      | 0.78                             | 1.56                                 | 62      | 0.20                             | 0.20                                 |
| 45 | 43      | 0.20                             | 0.39                                 | 63      | 0.78                             | 0.78                                 |
|    | 44      | 1.56                             | 1.56                                 | 64      | 0.20                             | 0.78                                 |
|    | 45      | 0.39                             | 0.20                                 | 65      | 0.39                             | 0.78                                 |
| 50 | 46      | 0.05                             | 0.20                                 | 66      | 0.10                             | 0.78                                 |
|    | 47      | 0.20                             | 0.39                                 | 67      | 1.56                             | 0.78                                 |
|    | 48      | 0.39                             | 0.20                                 | 68      | 0.10                             | 0.39                                 |
|    | 49      | 0.05                             | 0.39                                 | 69      | 0.10                             | 0.20                                 |
| 55 | 50      | 0.78                             | 1.56                                 | 70      | 1.56                             | 0.39                                 |
|    | 51      | 0.10                             | 0.39                                 | 71      | 0.20                             | 0.39                                 |

# (continued)

Ex. No. Anti-Candida Ex. No. Anti-Candida Anti-Aspergillus Anti-Aspergillus Activity (µg/mL) Activity (µg/mL) Activity (µg/mL) Activity (µg/ml) 52 0.39 0.39 72 6.25 12.5 53 0.20 0.20 73 0.10 0.39 54 0.10 0.39 74 0.10 0.20 0.78 0.05 0.10 75 0.20 56 1.56 >25 76 1.56 1.56 57 0.05 0.20 77 0.20 0.39 58 0.78 0.10 78 0.78 1.56 59 0.39 0.39 79 1.56 6.25 60 0.20 1.56 80 0.20 0.78

20 TABLE 3

|    | Ex. No. | Anti-Candida<br>Activity (µg/mL) | Anti-Aspergillus<br>Activity (µg/mL) | Ex. No. | Anti-Candida<br>Activity (µg/mL) | Anti-Aspergillus<br>Activity (µg/mL) |
|----|---------|----------------------------------|--------------------------------------|---------|----------------------------------|--------------------------------------|
|    | 81      | 0.20                             | 0.39                                 | 101     | 1.56                             | 1.56                                 |
| 25 | 82      | 0.20                             | 0.39                                 | 102     | 0.20                             | 0.39                                 |
|    | 83      | 0.20                             | 0.20                                 | 103     | 1.56                             | 0.78                                 |
|    | 84      | 3.13                             | >25                                  | 104     | 0.78                             | 0.78                                 |
| 30 | 85      | 1.56                             | 3.13                                 | 105     | 0.20                             | 0.20                                 |
|    | 86      | 0.05                             | 0.20                                 | 106     | 0.78                             | 0.20                                 |
|    | 87      | 0.20                             | 0.78                                 | 107     | 0.78                             | 0.78                                 |
|    | 88      | 0.20                             | 0.20                                 | 108     | 1.56                             | 3.13                                 |
| 35 | 89      | 0.39                             | 0.20                                 | 109     | 0.39                             | 0.78                                 |
|    | 90      | 1.56                             | 0.39                                 | 110     | 0.78                             | 0.78                                 |
|    | 91      | 0.20                             | 0.10                                 | 111     | 0.39                             | 0.78                                 |
| 40 | 92      | 0.39                             | 0.39                                 | 112     | 0.78                             | 0.39                                 |
|    | 93      | 0.20                             | 1.56                                 | 113     | 0.10                             | 0.20                                 |
|    | 94      | 0.78                             | 0.39                                 | 114     | 6.25                             | 6.25                                 |
|    | 95      | 0.39                             | 1.56                                 | 115     | 0.10                             | 0.20                                 |
| 45 | 96      | 3.13                             | 0.78                                 | 116     | 0.78                             | 0.20                                 |
|    | 97      | 0.39                             | 0.20                                 | 117     | 1.56                             | 0.78                                 |
|    | 98      | 0.39                             | 0.39                                 | 118     | 0.78                             | 3.13                                 |
| 50 | 99      | 3.13                             | 0.78                                 | 119     | 0.39                             | 0.78                                 |
|    | 100     | 3.13                             | 6.25                                 | 120     | 0.39                             | 0.20                                 |

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# TABLE 4

|    | TABLE 4 |                                  |                                      |         |                                  |                                      |
|----|---------|----------------------------------|--------------------------------------|---------|----------------------------------|--------------------------------------|
|    | Ex. No. | Anti-Candida<br>Activity (µg/mL) | Anti-Aspergillus<br>Activity (µg/mL) | Ex. No. | Anti-Candida<br>Activity (µg/mL) | Anti-Aspergillus<br>Activity (μg/mL) |
| 5  | 121     | 0.39                             | 0.78                                 | 141     | 0.39                             | 0.20                                 |
|    | 122     | 1.56                             | 0.78                                 | 142     | 0.39                             | 0.39                                 |
|    | 123     | 0.20                             | 0.39                                 | 143     | 0.39                             | 0.78                                 |
| 10 | 124     | 0.20                             | 0.39                                 | 144     | 0.39                             | 0.20                                 |
| 10 | 125     | 0.10                             | 0.39                                 | 145     | 6.25                             | 12.5                                 |
|    | 126     | 1.56                             | 0.39                                 | 146     | 6.25                             | >25                                  |
|    | 127     | 0.78                             | 1.56                                 | 147     | 1.56                             | 1.56                                 |
| 15 | 128     | 0.20                             | 0.39                                 | 148     | 0.20                             | 0.20                                 |
|    | 129     | 0.20                             | 0.20                                 | 149     | 6.25                             | 1.56                                 |
|    | 130     | 1.56                             | 0.20                                 | 150     | 0.39                             | 0.78                                 |
| 20 | 131     | 0.20                             | 0.20                                 | 151     | 0.78                             | 0.39                                 |
|    | 132     | 3.13                             | 3.13                                 | 152     | 0.78                             | 0.39                                 |
|    | 133     | 0.20                             | 0.39                                 | 153     | 1.56                             | 0.39                                 |
|    | 134     | 0.39                             | 0.78                                 | 154     | 0.78                             | 1.56                                 |
| 25 | 135     | 0.78                             | 0.39                                 | 155     | 0.10                             | 0.10                                 |
|    | 136     | 0.20                             | 0.20                                 | 156     | 0.20                             | 0.20                                 |
|    | 137     | 0.78                             | 1.56                                 | 157     | 3.13                             | 0.78                                 |
| 30 | 138     | 0.78                             | 0.78                                 | 158     | 1.56                             | 3.13                                 |
|    | 139     | 1.56                             | >25                                  | 159     | 0.78                             | 3.13                                 |
|    | 140     | 0.20                             | 0.78                                 | 160     | 0.39                             | 0.78                                 |
|    |         |                                  |                                      |         |                                  |                                      |

35 TABLE 5

|    | Ex. No. | Anti-Candida<br>Activity (µg/mL) | Anti-Aspergillus<br>Activity (µg/mL) | Ex. No. | Anti-Candida<br>Activity (μg/mL) | Anti-Aspergillus<br>Activity (µg/mL) |
|----|---------|----------------------------------|--------------------------------------|---------|----------------------------------|--------------------------------------|
| 40 | 161     | 0.39                             | 0.39                                 | 181     | 1.56                             | 0.39                                 |
|    | 162     | 0.78                             | 0.39                                 | 182     | >25                              | 0.20                                 |
|    | 163     | 3.13                             | 1.56                                 | 183     | 0.20                             | 0.78                                 |
|    | 164     | 6.25                             | 6.25                                 | 184     | >25                              | 0.39                                 |
| 45 | 165     | 0.78                             | 1.56                                 | 185     | 0.78                             | 0.78                                 |
|    | 166     | 0.39                             | 0.78                                 | 186     | 3.13                             | 0.78                                 |
|    | 167     | 1.56                             | 0.78                                 | 187     | 1.56                             | 0.78                                 |
| 50 | 168     | 0.78                             | 0.78                                 | 188     | 1.56                             | 0.78                                 |
|    | 169     | 0.39                             | 0.39                                 | 189     | 0.05                             | 0.20                                 |
|    | 170     | 0.78                             | 0.39                                 | 190     | 0.78                             | 0.78                                 |
|    | 171     | 0.20                             | 0.39                                 | 191     | 0.20                             | 0.39                                 |
| 55 | 172     | 6.25                             | 12.5                                 | 192     | 0.39                             | 1.56                                 |
|    | 173     | 1.56                             | 0.78                                 | 193     | 0.78                             | 0.78                                 |

## (continued)

| Ex. No. | Anti-Candida<br>Activity (µg/mL) | Anti-Aspergillus<br>Activity (µg/mL) | Ex. No. | Anti-Candida<br>Activity (μg/mL) | Anti-Aspergillus<br>Activity (μg/mL) |
|---------|----------------------------------|--------------------------------------|---------|----------------------------------|--------------------------------------|
| 174     | 6.25                             | 1.56                                 | 194     | 1.56                             | 3.13                                 |
| 175     | 0.78                             | 1.56                                 | 195     | 0.39                             | 0.78                                 |
| 176     | 0.20                             | 0.20                                 | 196     | 6.25                             | 6.25                                 |
| 177     | 0.39                             | 0.78                                 | 197     | 3,13                             | 1.56                                 |
| 178     | 0.39                             | 0.20                                 | 198     | 0.78                             | 1.56                                 |
| 179     | 0.78                             | 0.39                                 | 199     | 3.13                             | 6.25                                 |
| 180     | 0.39                             | 1.56                                 | 200     | 3.13                             | 3.13                                 |

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## TABLE 6

| Ex. No. | Anti-Candida<br>Activity (µg/mL) | Anti-Aspergillus<br>Activity (µg/mL) | Ex. No. | Anti-Candida<br>Activity (μg/mL) | Anti-Aspergillus<br>Activity (µg/mL) |
|---------|----------------------------------|--------------------------------------|---------|----------------------------------|--------------------------------------|
| 201     | 0.78                             | 0.39                                 | 215     | 0.39                             | 0.78                                 |
| 202     | 0.05                             | 0.20                                 | 216     | 0.39                             | 0.39                                 |
| 203     | 0.20                             | 1.56                                 | 217     | 0.10                             | 0.20                                 |
| 204     | 0.20                             | 0.39                                 | 218     | 0.20                             | 0.10                                 |
| 205     | 0.39                             | 0.78                                 | 219     | 3.13                             | 3.13                                 |
| 206     | 0.10                             | 0.39                                 | 220     | 6.25                             | 6.25                                 |
| 207     | 25                               | 6.25                                 | 221     | 1.56                             | 0.39                                 |
| 208     | 6.25                             | 0.78                                 | 222     | 0.39                             | 0.39                                 |
| 209     | 0.20                             | 0.39                                 | 223     | 0.39                             | 0.39                                 |
| 210     | 0.10                             | 0.20                                 | 224     | 0.39                             | 0.20                                 |
| 211     | 0.39                             | 0.39                                 | 225     | 0.78                             | 3.13                                 |
| 212     | 0.78                             | 0.78                                 | 226     | 0.39                             | 0.39                                 |
| 213     | 6.25                             | 1.56                                 | 227     | 1.56                             | 1.56                                 |
| 214     | 0.39                             | 0.39                                 | 228     | 0.78                             | 0.78                                 |

# 2. Experimental systemic candidal infection model in mice

# (1) Preparation of fungal inoculant

[1687] A standing culture of C. albicans E81022 strain was carried out for 48 hours at 30°C in sabouraud dextrose agar medium (SDA), the recovered fungal cells were suspended in sterilized physiological saline. By counting the fungal number on cytometry plate, the suspension was diluted to 2 ×107 cells / mL with sterilized physiological saline to serve fungal inoculum.

# (2) Infection

[1688] The fungal inoculum was used in the amounts of 0.2 mL to inoculate 4.5 to 5.5 week-old female ICR mice in the tail vein (4 x 106 cells/mouse).

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## (3) Treatment

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[1899] From 0.5 to 1 hour after fungal inoculation, 0.2 mL of agent solution (dissolved or suspended in sterilized physiological saline containing 6.5% dimethy sultoxide and 3.5% tween 80) was administered into the stornach using a peroral probe, 3 times every 4 hours. The agent concentration was 2.5 mg/kg or 10 mg/kg, and the number of animals in one group was 5 animals.

## (4) Determination of effects

10 [1690] The protective effect was determined by observing life/death until 14 days after infection and calculating the mean survival days.

[1691] As a result, as shown in Tables 7 and 8, mice administered with the compounds of the present invention survived for a long time as compared to the untreated group, and the compounds according to the present invention have been also found to demonstrate anti-Candida activity in vivo.

TABLE 7

| Mean Survival Days |                                 |          |         |
|--------------------|---------------------------------|----------|---------|
| Example Nos.       | Non-Adminstered Group (control) | 2.5mg/kg | 10mg/kg |
| 1                  | 4.0                             | 12.2     | 14.0    |
| 2                  | 4.0                             | 13.2     | 14.0    |
| 9                  | 3.4                             | 12.8     | 14.0    |
| 11                 | 2.6                             | 8.2      | 13.6    |
| 12                 | 2.6                             | 10.8     | 14.0    |
| 13                 | 6.0                             | 13.8     | 14.0    |
| 14                 | 4.0                             | 13.4     | 14.0    |
| 15                 | 2.6                             | 10.8     | 12.6    |
| 16                 | 4.0                             | 4.8      | 12.8    |
| 17                 | 4.0                             | 8.2      | 13.0    |
| 24                 | 2.6                             | 7.4      | 14.0    |
| 25                 | 2.6                             | 12.2     | -       |
| 27                 | 2.6                             | 3.0      | 10.0    |
| 29                 | 3.2                             | -        | 11.4    |
| 30                 | 6.0                             | 13.0     | -       |
| 31                 | 6.0                             | -        | 13.0    |
| 32                 | 6.0                             | 10.2     | 12.2    |
| 33                 | 6.0                             | 2.4      | 8.4     |
| 36                 | 6.0                             | 9.4      | 14.0    |
| 37                 | 6.0                             | 5.4      | 14.0    |
| 38                 | 6.0                             | 4.8      | 10.0    |
| 40                 | 4.0                             | 11.6     | 14.0    |
| 41                 | 4.0                             | 11.4     | 11.8    |
|                    |                                 |          |         |

TABLE 8

|              | Mean Survival Days              |          |         |  |  |  |
|--------------|---------------------------------|----------|---------|--|--|--|
| Example Nos. | Non-Adminstered Group (control) | 2.5mg/kg | 10mg/kg |  |  |  |
| 43           | 3.2                             | 10.6     | 14.0    |  |  |  |
| 45           | 3.2                             | 10.6     | 10.8    |  |  |  |
| 51           | 4.0                             | 13.5     | 14.0    |  |  |  |
| 52           | 4.0                             | 10.6     | 13.4    |  |  |  |
| 54           | 2.8                             | 13.0     | 13.6    |  |  |  |
| 55           | 2.8                             | 13.8     | 14.0    |  |  |  |
| 58           | 2.8                             | 3.8      | 12.0    |  |  |  |
| 62           | 1.4                             | 10.2     | -       |  |  |  |
| 73           | 2.2                             | 4.4      | 12.6    |  |  |  |
| 102          | 3.2                             | 13.2     | 13.0    |  |  |  |
| 104          | 3.2                             | 8.2      | 13.2    |  |  |  |
| 105          | 3.2                             | 5.4      | 12.8    |  |  |  |
| 109          | 2.8                             | 11.0     | 11.8    |  |  |  |
| 110          | 2.8                             | 12.0     | -       |  |  |  |
| 111          | 2.8                             | 13.6     | -       |  |  |  |
| 112          | 4.0                             | -        | 12.2    |  |  |  |
| 113          | 2.8                             | 13.0     | 14.0    |  |  |  |
| 115          | 2.8                             | 10.8     | 13.2    |  |  |  |
| 116          | 2.8                             | 4.6      | 12.6    |  |  |  |
| 120          | 2.8                             | 3.2      | 13.4    |  |  |  |
| 131          | 1.4                             | 12.6     | 12.8    |  |  |  |
| 133          | 2.2                             | 7.0      | 13.4    |  |  |  |
| 135          | 2.2                             | 11.0     | 13.4    |  |  |  |
| 151          | 2.4                             | 7.0      | 14.0    |  |  |  |
| 155          | 2.4                             | 10.4     | 13.0    |  |  |  |
| 166          | 2.8                             | 3.4      | 12.4    |  |  |  |
| 171          | 2.8                             | 8.4      | 12.6    |  |  |  |
| 176          | 4.2                             | 12.6     | 13.4    |  |  |  |
| 192          | 1.0                             | 3.2      | 9.4     |  |  |  |
| 202          | 1.0                             | 2.4      | 10.0    |  |  |  |

# Industrial Applicability

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[1892] According to the present invention, the compound (f) of the present invention or a sait thereof 1) acts against the onset, development and persistence of infections by inhibiting fungal GPI biosynthesis, thereby inhibiting expression of cell wall proteins and blocking cell wall assembly while preventing the fungus from attaching to cells so that the pathogen cannot become pathogenic, and 2) is superior in terms of physical properties, safety and metabolic stability, and is extremely useful as a preventive or therepeutic agent for fungal infections.

#### Claims

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#### 1. A compound represented by the following formula (I), or a salt thereof:

wherein R1 represents a hydrogen atom, a halogen atom, an amino group, R1-NH-(wherein R11 represents a  $C_{LB}$  alikyl group, a hydroxy  $C_{LB}$  alikyl group, a  $C_{LB}$  alikyl group,  $C_{LB}$  alikyl group, a  $C_{LB}$  al

ring A represents a 5- or 6-member heteroaryl ring or a benzene ring which may have 1 or 2 halogen atoms, or 1 or 2 C<sub>1-6</sub> alkyl groups;

Z represents a single bond, a methylene group, an ethylene group, an oxygen atom, a sulfur atom, -CH<sub>2</sub>O-, -OCH<sub>2</sub>·, -NH-, -CH<sub>2</sub>NH-, -NHCH<sub>2</sub>·, -CH<sub>3</sub>S-, or -SCH<sub>2</sub>·;

 $\mathbb{R}^3$  represents a hydrogen atom, a halogen atom, a  $\widetilde{C}_{1-6}$  allyl group, a  $C_{2-6}$  cycloallyl group, a  $C_{6-10}$  aryl group, a 5- or 6-member heteroaryl group, -5- or 6-member heteroaryl group, -5- or 6-member heteroaryl group, a -5- or 6-m

[substituent group α]

substituent group  $\alpha$  represents the group consisting of a halogen atom, a cyano group, a  $C_{1,a}$  alkyl group, a  $C_{1,b}$  alkoxy group, a  $C_{1,b}$  alkoxy group, a  $C_{1,b}$  alkoxy group and a  $C_{2,b}$  alkynyl group group group.

R4 represents a hydrogen atom or a halogen atom;

excluding compounds where all of  $R^1$ ,  $R^2$ , and  $R^4$  represent the hydrogen atom at the same time when Z represents the signle bond or  $R^3$  represents the hydrogen atom.

2. The compound according to Claim 1 or the salt thereof, wherein a partial structure represented by formula (II):

in the compound represented by the formula (I):

is a partial structure selected from the group consisting of:

- The compound according to Claim 1 or the salt thereof, wherein one of X and Y is a nitrogen atom and the other is an oxygen atom.
- 4. The compound according to Claim 3 or the salt thereof, wherein a partial structure represented by the formula (II):

in the compound represented by the formula (I):

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is a partial structure represented by the following formula (III):

or a partial structure represented by the following formula (IV):

5. The compound according to Claim 1 or the salt thereof, wherein X and Y are both nitrogen atoms.

6. The compound according to Claim 5 or the salt thereof, wherein a partial structure represented by the formula (II):

in the compound represented by the formula (1):

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20 is a partial structure represented by the following formula (V):

or a partial structure represented by the following formula (VI):

- 7. The compound according to any one of Claims 1 to 6 or the salt thereof, wherein R2 represents an amino group.
- The compound according to Claim 7 or the salt thereof, wherein R<sup>1</sup> represents a hydrogen atom, an amino group or a C<sub>1-8</sub> alkoxy C<sub>1-8</sub> alkyl group.
- The compound according to any one of Claims 1 to 6 or the salt thereof, wherein R<sup>1</sup> represents an amino group and R<sup>2</sup> represents a hydrogen atom.
- 10. The compound according to any one of Claims 1 to 9 or the salf thereof, wherein the ring A represents a pyridine ring, a benzene ring, a furan ring, a thiophene ring or a pyrrole ring.
- 11. The compound according to Claim 10 or a salt thereof, wherein ring A represents a pyridine ring or a benzene ring.
- The compound according to any one of Claims 1 to 11 or the salt thereof, wherein Z represents an oxygen atom,
   -CH<sub>2</sub>O or -OCH<sub>2</sub>-.
  - 13. A pharmaceutical composition comprising the compound according to any one of Claims 1 to 12 or the salt thereof.

14. A medicament comprising the compound according to any one of Claims 1 to 12 or the salt thereof. 15. An antifungal agent comprising the compound according to any one of Claims 1 to 12 or the salt thereof, as an active ingredient. 16. A method for preventing and/or treating a fungal infection comprising administering a pharmacologically effective dose of the compound according to any one of Claims 1 to 12 or the salt thereof, 17. A use of the compound according to any one of Claims 1 to 12 or the salt thereof for manufacturing an antifungal agent.

# INTERNATIONAL SEARCH REPORT

International application No.

|                                                                                                                | INTERNATIONAL SEARCH REPORT                                                                                                                                                                                                                                                     | mic                                                                                                                                                                                            | пынова аррисация №о.                                                                                                                                                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| v Clveens                                                                                                      | CATION OF SUBJECT MATTER                                                                                                                                                                                                                                                        |                                                                                                                                                                                                | PCT/JP2006/321678                                                                                                                                                                                                                                                            |
| COVD401/0 A61P31/10 COVD413/1 According to Int B FIELDS SE                                                     | 74(2006.01)1, A51K31/4439(2006.0<br>7(2006.01)1, C07D491/14(2006.01<br>14(2006.01)1<br>emational Patent Classification (FC) or to both national                                                                                                                                 | ) i, CO7D413/04- I classification and IPC  assultation symbols)                                                                                                                                | (2006.01)i,                                                                                                                                                                                                                                                                  |
| C07D413/1                                                                                                      |                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                |                                                                                                                                                                                                                                                                              |
|                                                                                                                |                                                                                                                                                                                                                                                                                 | tsuyo Shinan Toro<br>roku Jitsuyo Shin                                                                                                                                                         |                                                                                                                                                                                                                                                                              |
| CAplus                                                                                                         | base consulted during the international search (name of (STN), RBGISTRY (STN)  NTS CONSIDERED TO BE RELEVANT                                                                                                                                                                    | data base and, where pract                                                                                                                                                                     | licable, search terms used;                                                                                                                                                                                                                                                  |
| Category*                                                                                                      | Citation of Jocument, with indication, where app                                                                                                                                                                                                                                | propriete, of the relevant p                                                                                                                                                                   | ussages Relevant to claim N                                                                                                                                                                                                                                                  |
| A                                                                                                              | JP 2004-529154 A (Torrent Ph<br>Ltd.),<br>24 September, 2004 (24.09.04)<br>Full text<br>& WO 2002/085897 Al & CA<br>& EP 1373263 Al & EP                                                                                                                                        | armaceuticals                                                                                                                                                                                  | 1-25,17                                                                                                                                                                                                                                                                      |
| A                                                                                                              | US 2003/0114491.Al (Korea In and Technology), 19 June, 2003 (19.06.03), Full text & US 6759419 B2 & KR                                                                                                                                                                          | stitute of Sci<br>2003034822 A                                                                                                                                                                 | ence 1-15,17                                                                                                                                                                                                                                                                 |
| × Further d                                                                                                    | ocuments are listed in the continuation of Box C.                                                                                                                                                                                                                               | See patert family                                                                                                                                                                              | mncx.                                                                                                                                                                                                                                                                        |
| 'A' document dibe of parties 'B' earlier applied to the document of either to est special reas 'O' document si | which may throw doubts on priority claim(s) or which is<br>ablish the problection date of another citation or other<br>to (as specified)<br>eleming to in call decisioner, use, eithebition or other means<br>abbished more to the international filing date but later than the | date and not in conflict<br>the principle of theory is<br>"X" document of particular<br>considered novel or or<br>step when the documen<br>"Y" document of particular<br>considered to involve | relevance: the chumed invention cannot be<br>annot be considered to involve an invent, wi<br>it taken alone<br>relevance; the claimed inventior cannot be<br>an inventive step when the document is<br>note other such documents, such combination<br>on shilled in the set. |
|                                                                                                                | al completion of the international search<br>ember, 2006 (11.12.06)                                                                                                                                                                                                             | Date of mailing of the in<br>19 December                                                                                                                                                       | ternational search report<br>r, 2006 (19.12.06)                                                                                                                                                                                                                              |
|                                                                                                                | ng address of the ISA/<br>se Patent Office                                                                                                                                                                                                                                      | Authorized officer                                                                                                                                                                             |                                                                                                                                                                                                                                                                              |
| Faccimile No.                                                                                                  |                                                                                                                                                                                                                                                                                 | Telephone No.                                                                                                                                                                                  |                                                                                                                                                                                                                                                                              |

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Form PCT/ISA/210 (continuation of second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No PCT/JP2006/321678

| Box No. II         | Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)                                                                                                                                                                                           |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. X Claim because | Isoarch report has not beer established in respect of certain claims under Article 17(240) for the following reasons:  1800: 16 to they relate to subject matter not required to be secrebed by this Authority, namely.  15 pertains to methods for treatment of the human body by therapy. |
| becaus             | i Nos.  e they relate to parts of the international application that do not comply with the prescribed requirements to such an that no meaningful international secrets can be carried out, specifically:                                                                                   |
| 3. Claum because   | t Nos : they are dependent claims and are not drafted in accordance with the scored and third sentences of Rule 6.4(a).                                                                                                                                                                     |
| Box No. III        | Observations where unity of invention is lacking (Continuation of item 3 of first sheet)                                                                                                                                                                                                    |
|                    |                                                                                                                                                                                                                                                                                             |
| 1. As all claims   | required additional search fees were timely paid by the applicant, this international search report covers all searchable.                                                                                                                                                                  |
|                    | searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of<br>ditional fee.                                                                                                                                                  |
|                    | some of the required additional starch fees were timely pool by the applicant, this international search report covers<br>ose claims for which form were pand, specifically claims Nos.:                                                                                                    |
|                    | piled additional search fees were timely peal by the applicant. Consequently, this international search report is<br>sed to the invention first mentioned in the claims; it is covered by clausa Nos.                                                                                       |
| Remark on Pr       | payment of a protest fee.                                                                                                                                                                                                                                                                   |
|                    | The additional search fees were accompanied by the applicant's protest but the applicable protest<br>fee was not paid within the time limit specified in the invitation.                                                                                                                    |
| BOTTO 4 4          | No protest accompanied the payment of additional search fees.                                                                                                                                                                                                                               |

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)

## REFERENCES CITED IN THE DESCRIPTION

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